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CORTICAL D.C. CHANGES INCIDENT TO MIDLINE THALAMIC STIMULATION [1]

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Prior studies by D.C. recording have shown that cortical after-effects having a duration of one second or more can follow the evoked response and spontaneously recurring strychnine or veratrine spikes (Goldring and O'Leary 1951; 1954, a and b). Summation of such after-effects has also been demonstrated during repetitive stimulation of optic nerve and lateral geniculate nucleus, or with spontaneously appearing clusters of strychnine or veratrine spikes. To date we have noted that the polarity of after-effect is usually the same as that of the principal phase of the evoked response or spontaneous spike transient which precedes it. Thus, a negative after-effect follows the principally negative strychnine spike, and a positive one, the positive veratrine spike. In the case of the diphasic evoked response (visual cortex) the after-effect may be diphasic (positive followed by negative), or principally positive or negative. The latter variability is believed to result from the algebraic summation of oppositely directed positive and negative components which differ in their amplitude under different circumstances. Such a view is strengthened by observations made during anoxia, in systemic failure, and subsequent to periods of convulsive discharge in the experimental animal. In these instances the evoked visual response becomes a positive transient due to disappearance of the more labile succeeding negative wave. As it does so, after-effect positivity increases if the change had been positive previously, or becomes positive if it had been diphasic or negative (Goldring, O'Leary and Lam 1954).

Beyond identifying these cortical after-effects as concomitants of neural activity, their relation to the quick transients is not clear at present. For example, neither positive nor negative after-effect has been observed to change excitability as inferred from the amplitude of succeeding transients. Several alternative propositions concerning after-effect need consideration. It may be: an active neural process different from that which occasions the evoked response (as is the after-potential of peripheral nerve); primary activity continuing beyond the duration of the transients studied conventionally by capacity-

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coupled amplifiers; a slow recovery of the resting state by re-polarization; or a field potential having an origin somehow different from the activity which occasions the preceding transient.

The above considerations suggest the importance of examining transients other than the evoked response using D.C. recording techniques. Cortical recruiting (Dempsey and Morison 1942) has proved very satisfactory for this purpose. The latter may be elicited by low frequency stimulation, whereas high frequency stimulation (30-100/sec.) at the same parameters results in "activation" (Magoun 1956). Furthermore, the continuance into the post-stimulatory period of the D.C. change which accompanies a recruiting series makes this preparation ideal for examining the relation between cortical after-effect and excitability. Finally convulsoid activity may develop during prolonged stimulation of the mid-line thalamus. This permits comparing D.C. changes which accompany paroxysm initiated from the thalamic intralaminar nuclei with the D.C. shifts which appear during convulsoid discharge initiated from thalamic relay nuclei.

METHODS

Observations were made upon 25 rabbits and 10 cats. These were carried under light anesthesia or in an unanesthetized state. For the latter, after preliminary etherization, the cat was decerebrated; and the cord of the rabbit was transected at C-5. Recordings were commenced two hours after termination of anesthesia, bipolar stimulating electrodes being used. The latter were 75 μ in diameter, insulated to their tips and having a tip separation of 75-100 μ. A Grass stimulator delivering 30 V., 0.1 msec. at 6/sec. or higher frequency was used routinely.

Recording was transcortical (surface reference convention) utilizing non-polarizable calomel half-cells. In the rabbit records were obtained chiefly from precentral granular cortex but in several instances from the visual cortex instead. With one exception (gyrus proreus) records from the rostral cortex of the cat were obtained from the anterior suprasylvian gyrus. Stimulating electrodes were introduced routinely into the nucleus centralis or paracentralis of the rabbit and VA (ventralis anterior) of the cat with the sole object of selecting a point from which a low threshold recruiting response could be obtained. The tip was electrolyzed later and its position checked histologically. A capacity coupled electroencephalograph was used to monitor the SP (steady potential) across the cortex by short-circuiting the input 8 times per second. A potentiometer in series with animal and amplifier served to balance the initial and any subsequently developing potential difference across the cortex, and the counter-voltage necessary to achieve a balance could then be read directly from the potentiometer. Details are provided in a previous study (Goldring and O'Leary 1951). A D.C. amplifier, oscillograph and camera were used to record the recruiting transients and accompanying D.C. change.

RESULTS

1. *D.C. Change Associated with Cortical Recruiting.* The response to a single stimulus given the intralaminar nuclei of the rabbit thalamus is relatively low voltage positive-negative transient, and this is followed by a negative after-effect having a duration of 200-300 msec. The latter part of this after-effect may be followed by 10-12/sec. waves (fig. 1 A). A second stimulus delivered during the after-negativity results in a higher voltage transient in which the negative (recruiting) component shows significantly increased voltage (fig. 1 B and C). The size of the second transient bears no relation to the after-negativity voltage (compare second responses in fig. 1 E and C), but does relate to the frequency of stimulation.

In the rabbit the optimum stimulus frequency for recruiting is 5-6/sec. As the frequency is increased from 1-6/sec. there is summation of the negative after-effects of individual transients; at 6/sec. it is not unusual for a 500 μV. D.C. shift to develop and outlast the stimulus period by 1-2 sec. (fig. 1 B-F). In some experiments (rabbit) the negative recruiting wave is followed by a lower positive one which endures from 0.8 to 1.0 sec. In these instances the negative D.C. shift which accompanies the recruiting series is a relatively minor one.

In the decerebrate cat stimulation of VA usually elicited a recruiting series like those seen in rabbits in which the recruiting wave was followed by a positive after-effect. With repetitive stimulation at 6-10/sec. either no

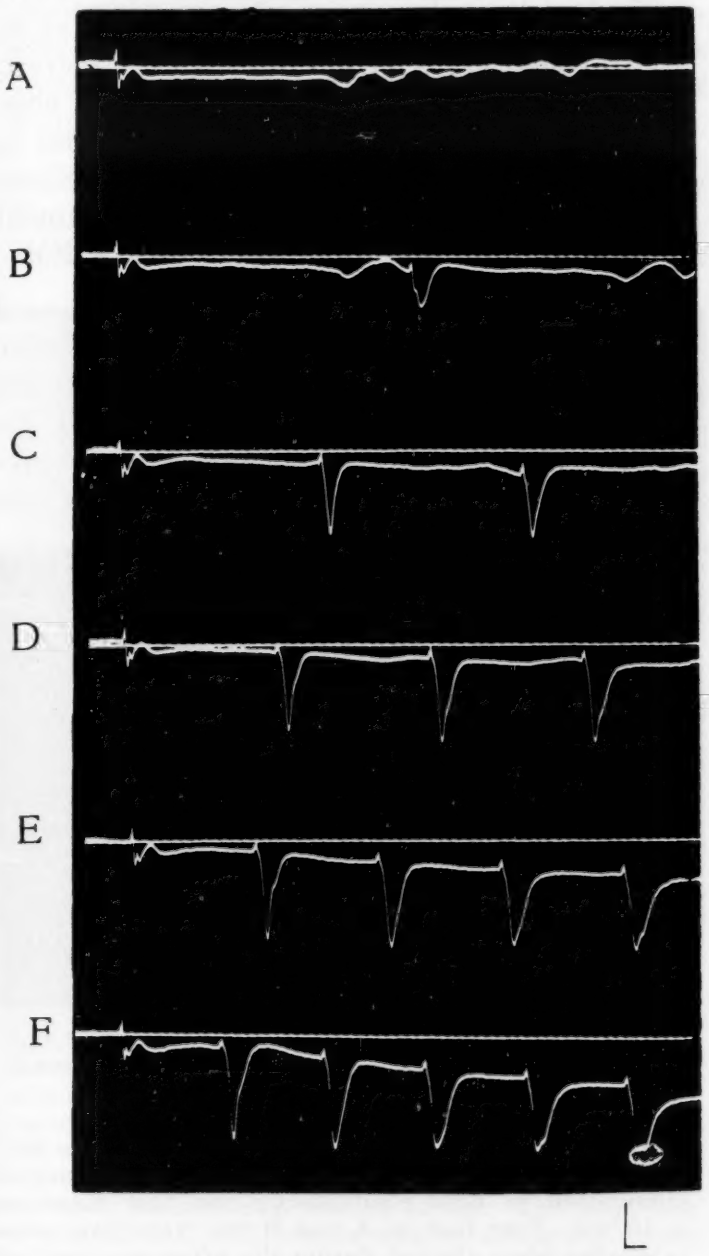

Fig. 1

D.C. change associated with cortical recruiting in the rabbit. A-E, increasing frequencies of stimulation from 1-6/sec. Note that it is the negative after-effect seen in A, which summates to produce the D.C. shift observed with repetitive stimulation in C-F. Vertical line of right angle = 500 μV.; horizontal line = 20 msec. In all figures negative polarity is down.

subsequent D.C. change or a slight positive shift accompanies cortical recruiting (fig. 3 A and B). The positive change was shown to be due to a summation of third positive phases which follow each negative component during low frequency recruiting. With high frequency stimulation these positivities become obliterated. The result is that a negative D.C. change now develops during the period of stimulation (fig. 3 E).

Under apparently normal circumstance recruiting was seen occasionally in which the

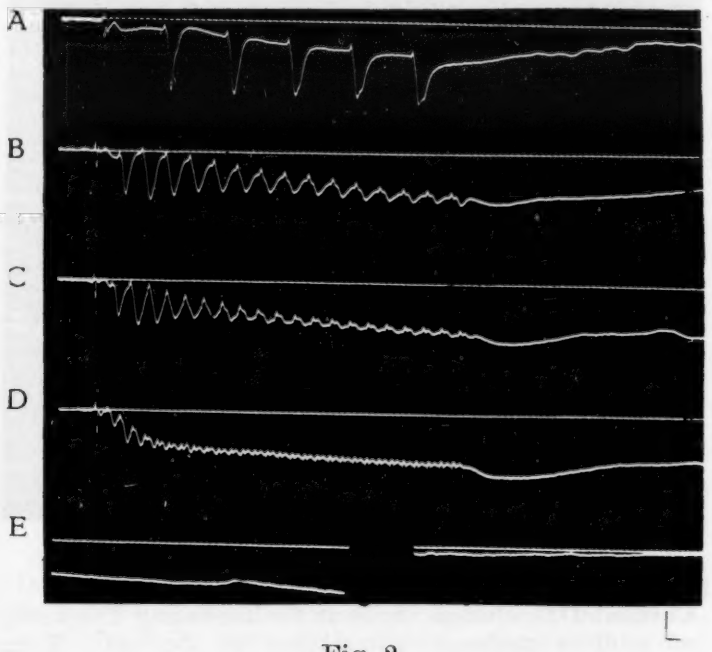

Fig. 2

Cortical D.C. change incident to increasing frequency of midline thalamic stimulation in the rabbit. A = 6/sec., B = 15/sec., C = 20/sec., D = 30/sec. E is a continuation of the record in D. Period of stimulation in A through D is one sec. Break in line in E represents time interval of 5 sec. Vertical line of right angle = 500 μV.; horizontal line = 20 msec.

principal wave components were positive in polarity. In these instances the D.C. change which accompanied recruiting was also positive. To obtain more data for establishing correlations between polarity of recruiting response and of the accompanying D.C. change, veratrine 10^{-4} was applied to the surface of rabbit cortex. It was chosen because in prior studies (Goldring and O'Leary 1954) it caused conversion of the diphasic evoked response and of negatively spiked barbiturate spindles to positively directed components. In the present instance veratrine, applied to an area from which negative recruiting waves and an associated negative D.C. change were obtained, converted both recruiting transients and the D.C. accompanient to positive polarity.

2. *Cortical D.C. Change Incident to Increasing Frequency of Midline Thalamic Stimulation.* Raising the frequency above 10/sec.

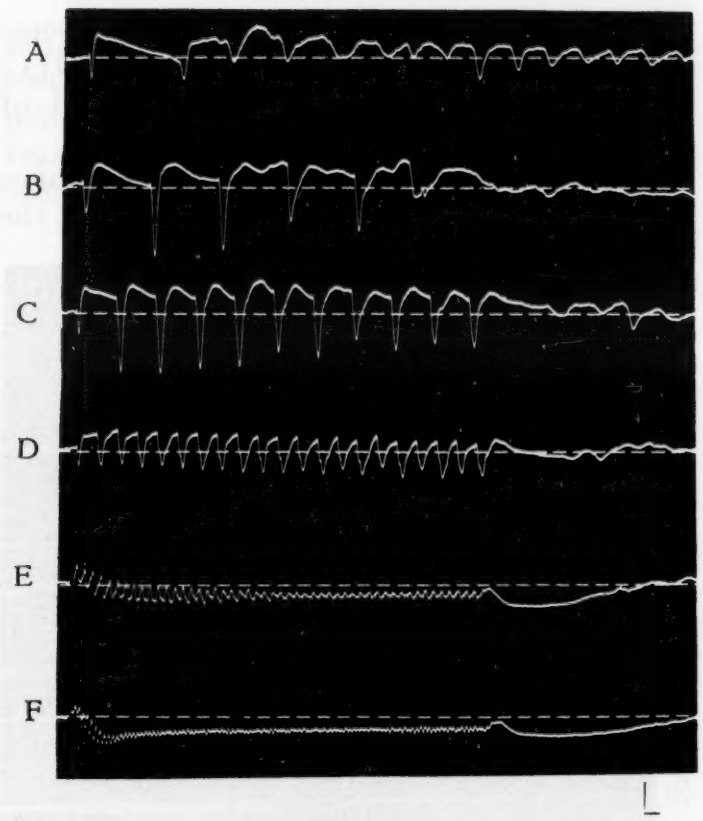

Fig. 3

Cortical D.C. change incident to increasing frequency of midline thalamic stimulation in the cat. A = 1/sec., B = 6/sec., C = 10/sec., D = 20/sec., E = 50/sec., F = 100/sec. In A, a 10/sec. spindle follows the response to a single stimulus. Period of stimulation in B through F is one sec. Vertical line in right angle is 500 μV.; horizontal line is 20 msec.

(rabbit) and also beyond that which produces optimum recruiting increases the amplitude and duration of D.C. change. When the intralaminar nuclei were stimulated for 1 sec. at 30/sec. a negative D.C. shift of as much as 1 mV. might occur, that change persisting for as long as 5-7 sec. into the post-stimulatory period (fig. 2, D and E). Even though the single responses to repetitive stimulation at this frequency became reduced to negligible amplitude, the usual cortical ECG was "activated" (Magoun 1956) during the D.C. shift.

In rabbit experiments in which the recruiting wave showed a terminal positive component on low frequency stimulation, and in cats where that was usually the case, the negative D.C. shift was not nearly so prominent with stimuli at 30/sec. or more (fig. 3 F).

3. *Cortical D.C. Change Incident to Prolonged Stimulation of the Midline Thalamus.* Stimulation of the intralaminar nuclei for periods as long as 10-15 sec. at frequencies of 15-20/sec. caused the D.C. shift to become progressively less evident as stimulation was continued, the D.C. approaching the pre-stimulatory SP. In this circumstance there was a positive rebound at the end of stimulation and this could last 20-30 sec. into the post-stimulatory period (fig. 4). During the after-positivity the ECG showed a low voltage pattern. The above described pattern of D.C. change with prolonged stimulation was much more common in the cat where the immediate

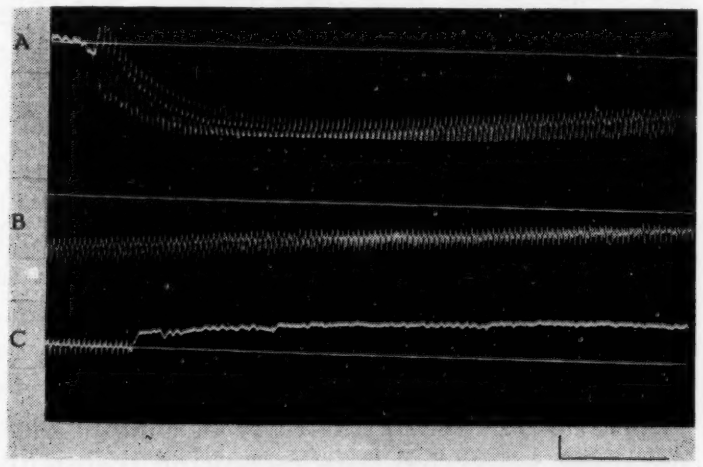

Fig. 4

Cortical D.C. change incident to prolonged stimulation of the midline thalamus in the cat. Frequency of stimulation is 15/sec. B is a continuation of the record shown in A. A 3 sec. strip of record has been omitted between B and C. Vertical line of right angle is 500 μV.; horizontal line is one sec.

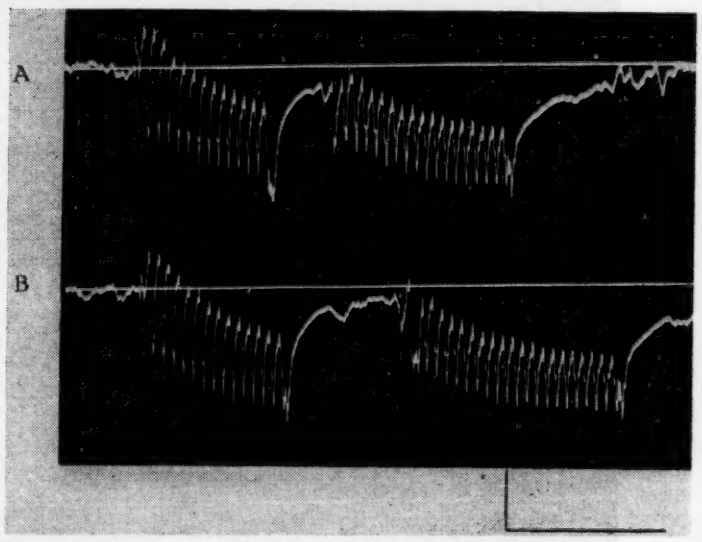

Fig. 5

Excitability of cortical neurones during negative D.C. change. Record is taken from the cat. Frequency of stimulation in both conditioning and test responses is 15/sec. Note that in A and B the recruiting series is smaller when elicited during the after-negativity of a preceding recruitment response. However, the first transient of the tested series is larger than the first of the conditioning one. Vertical line of right angle is 1 mV.; horizontal line is one sec.

response to a single stimulus was usually followed by a low voltage long-lasting positivity. In the rabbit, where the immediate response was more commonly followed by a negative after effect, the negative D.C. change with prolonged stimulation was also reduced. However, here the positive shift did not always appear in the post-stimulatory period, or if it did so, revealed itself as a minor change.

4. *Excitability of Cortical Neurones during Negative and Positive D.C. Changes.* Excitability was examined by occasioning a test

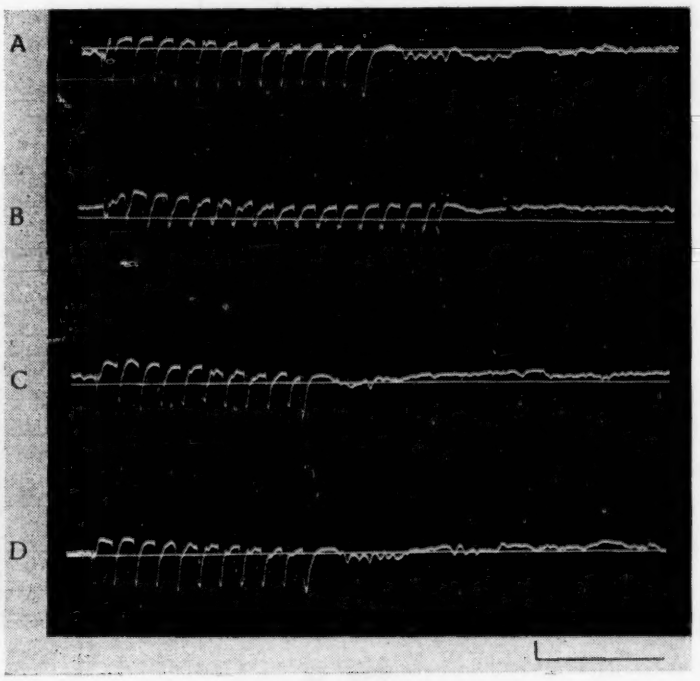

Fig. 6

Excitability of cortical neurones during positive D.C. change. Record is taken from cat. Frequency of stimulation in A through D is 6/sec. A is a control recruiting response. B, marked decrease in size of response during the start of a positive D.C. shift which followed a 12 sec. period of stimulation of the midline thalamus at a rate of 15/sec. The amplitude of positive D.C. shift can be seen by noting the degree of separation between the line upon which the transients are written and the horizontal straight line representing the pre-stimulatory base-line. C, partial recovery in size of the recruiting series as the positive D.C. shift decreases in amplitude. D, complete recovery of the tested response with return of the positive D.C. shift to the pre-stimulatory base-line. Vertical line of right angle = 500 μV.; horizontal line = 1 sec.

recruiting series during the after-negativity which followed a preceding conditioning recruitment, and also during the positive D.C. shift incident to prolonged stimulation of the intralaminar nuclei. In all instances the amplitude of each test was compared with that of the conditioning series. The amplitude was

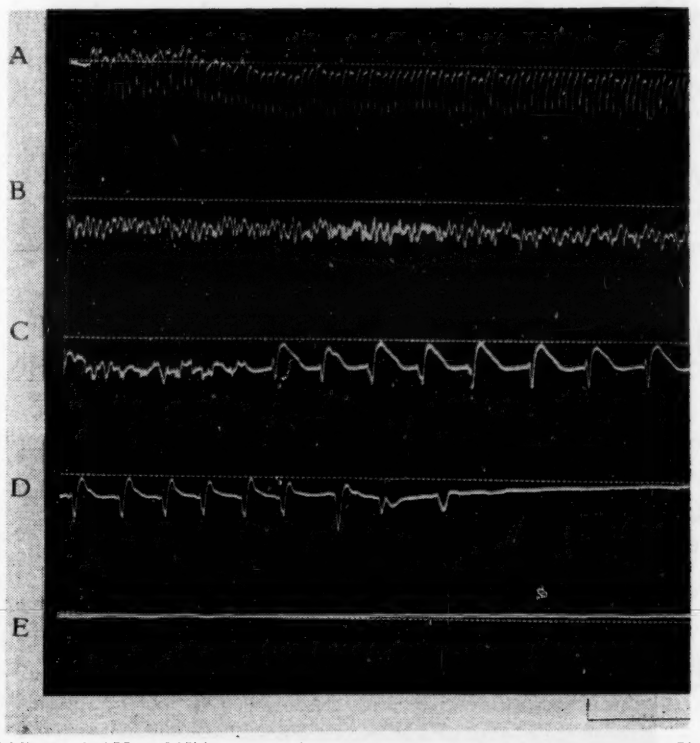

Fig. 7

D.C. change accompanying cortical paroxysm induced by repetitive stimulation of V A nucleus in cat. A, negative D.C. shift with 20/sec. stimulation. A 3 sec. strip of record has been omitted between A and B. B, with continuation of stimulation there is an increase in negative D.C. change. C, upon cessation of stimulation (white dot) high voltage paroxysmal activity is in evidence and the steady potential remains shifted negatively. D, return of steady potential to the pre-stimulatory base-line with termination of paroxysm. E, positive shift of steady potential in the post-stimulatory iso-electric period. Vertical line of right angle = 500 μV.; horizontal line = 1 sec.

reduced during the post-stimulatory shift and returned toward normal as the SP approached its prestimulatory level (fig. 5 and 6). During a test series introduced during a negative D.C.

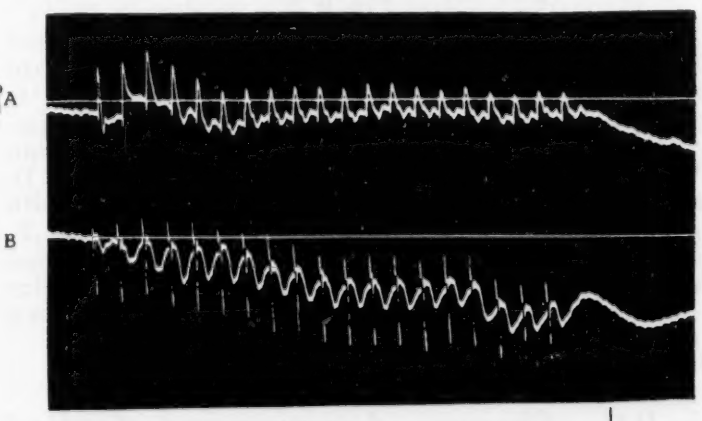

Fig. 8

Cortical D.C. change with repetitive stimulation of lateral geniculate nucleus (A) and nucleus paracentralis (B) in the rabbit. Frequency of stimulation is 20/sec. Vertical line in right angle = 50 μV.; horizontal line = 50 msec.

shift the first response was always larger than the first of a conditioning series, but the ensuing waves had a lower amplitude (fig. 5).

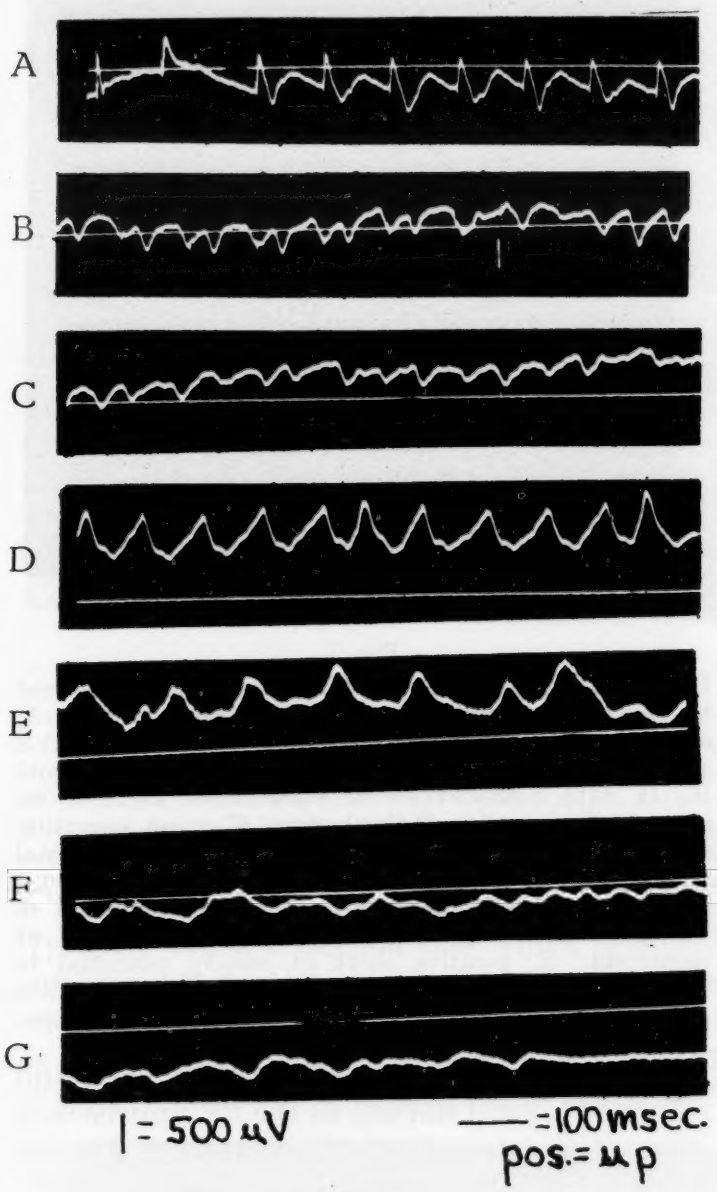

Fig. 9

D.C. change accompanying cortical paroxysm induced by repetitive stimulation of the lateral geniculate nucleus in the rabbit. Frequency of stimulation is 10/sec. A, no D.C. change during beginning of stimulation. B, SP shifts positively at end of stimulation which is identified by vertical white line. C and D, steady potential continues to shift positively with increase in voltage of paroxysmal activity. E and F, steady potential shifts towards base-line and then negatively as paroxysm ends. G, further negative shift in steady potential with appearance of iso-electric record in post-stimulatory period.

5. *D.C. Changes Accompanying Cortical Paroxysm Induced by Repetitive Intralaminar or VA Stimulation.* It was sometimes the case in either rabbit or cat that cortical paroxysm was initiated by stimulation. As the high voltage repetitive discharge continued into the post-stimulatory period, the SP shifted negatively and as the discharge became irregular and terminated SP returned towards the pre-stimulatory baseline. In the isoelectric period following the spike discharge SP crossed the baseline to shift positively but ultimately returned to its resting level as the ECG assumed its pre-stimulatory appearance (fig. 7). This sequence of changes is the opposite of that initiated by stimulation in the thalamic relay nuclei (Goldring and O'Leary 1951). In the latter instance SP was observed to shift positively during the paroxysm and to become negative with post-ictal suppression.

To verify this suggested difference between stimulation of midline and relay nuclei paroxysms were occasioned from both in the same rabbit. One pair of stimulating electrodes was placed in the nucleus paracentralis and the other in the lateral geniculate nucleus. Recording was done from the visual cortex. With stimulation of the lateral geniculate nucleus at 20/sec. either no D.C. or a minor positive one occurred during stimulation, but afterwards a negative change occurred lasting 0.5 to 1 sec. (fig. 8 A). If the period of stimulation lasted 5 to 15 sec. high voltage paroxysm was readily produced. This was accompanied by the usual positive change to relay nucleus stimulation. It became reduced

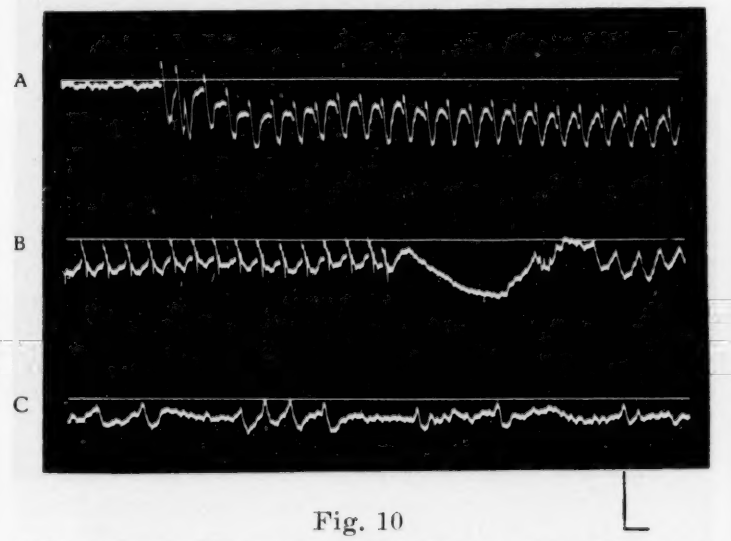

Fig. 10

D.C. change accompanying cortical paroxysm induced by repetitive stimulation of nucleus paracentralis in the rabbit. Frequency of stimulation is 20/sec. A, negative D.C. change with start of stimulation. B, upon cessation of stimulation a paroxysm is in evidence and the steady potential remains shifted negatively. C, continuation of paroxysmal activity accompanied by a negative D.C. change. Vertical line of right angle = 500 μV.; horizontal line = 50 msec.

as the paroxysm broke up and SP shifted negatively during the post-paroxysmal period (fig. 9). By contrast stimulation of the midline thalamus (20/sec. for 1 sec.) produced a negative D.C. shift (fig. 8 B), and prolonged stimulation (5-15 sec.) only occasionally resulted in paroxysm. When it did so the high voltage cortical discharge during the paroxysm was accompanied by a negative D.C. change (fig. 10).

DISCUSSION

In evaluating the significance of the usual negative D.C. shift with recruiting in the rabbit we are concerned with: (1) the part of the neurone in which it originates — i.e., apical dendrite, soma, axon —, and (2) the components of potential derived from the summation of transients as distinguished from those arising through after-effect summation. By analogy with peripheral nerve, where an after-potential may follow the all-or-none spike, we define after-effect in the present instance as any neural process occurring subsequent to the negative recruiting transient. It is a fair surmise that both nerve after-potentials and the after-effects reported upon herein have a similar origin, but so far their identity has not been established.

Clare and Bishop (1955, 1956) have indicated a dendritic origin for recruiting transients and in their study on apical dendrites showed a negative D.C. shift due to summation of transients with high frequency stimulation. Thus, when two stimuli are spaced so that the second is delivered within the time course of the response to the first stimulus (20 msec.), the dendrite is found to have no absolute refractory period and summation of graded response results. With repetitive stimulation at high frequencies the rising phase of each response may ensue at *the start* of the falling phase of the preceding one. The transients thus fuse into a relatively smooth curve, producing a persistent shift in the base line — *a D.C. shift*. Such a situation is evident in our record (fig. 2 D) where summated transient, incident to high frequency midline thalamic stimulation, are seen as a ripple on the negatively shifted base line. Utilizing the findings of Clare and Bishop we interpret this record as evidence for a steady state of activity in dendrites. Such a steady state could occlude other manifestations of dendritic functioning — for example, spontaneous activity. Thus, the record which results from high frequency stimulation, if recorded with capacity-coupled amplifiers, becomes "activation" in character (Magoun 1956); and we regard steady state as one factor in producing it.

Besides the contribution of transients to the D.C. shift we believe that after-effect summation is an important factor. Certainly, it alone accounts for the shift observed during low frequency stimulation where the temporal relationship of the transients precludes their summation (fig. 1). The persistence of D.C. shift into the post-stimulatory period is also best explained by summation of after-effect. Further, the minor positive shift in steady potential seen with recruitment in the cat and the failure in some animals to develop a major negative shift with high frequency stimulation finds a more ready explanation in summation of after-effects. Two polarities of after-effect can be shown to associate with recruiting response. The shortest lasting of these is the positive phase which follows immediately after the negative recruiting transient in the cortex of the cat and sometimes of the rabbit. When this component is evident, it is our interpretation that its summation at low frequency stimulation exceeds that of any coincident negative D.C. shift, the net result being a positive shift. With high frequency stimulation the positive component is obscured, and as this happens the expected negative shift develops. When positive after-effect is absent with low frequency stimulation, the negative D.C. shift with high frequency stimulation reaches a significantly greater amplitude than when it is present. Thus we infer that this component provides an opposing potential, even at high frequency, which sums with the dominant negative shift and by algebraic summation subtracts from it.

With long-sustained repetitive stimulation (10-15 sec.) the negative shift may recede toward the pre-stimulatory baseline and when stimulation is terminated under these circumstances the post-stimulatory period is characterized by a positive shift. The significance of these late effects cannot be assayed at this time.

The final consideration relates to convulsoid activity occurring during a negative D.C. shift in the case of repetitive intralaminar stimulation, as opposed to that appearing with a positive D.C. shift with repetitive stimulation in the thalamic relay nuclei. The difference cannot be related alone to the depth in the cortex at which the convulsoid activity develops. In the instance of intralaminar stimulation the convulsoid discharge would appear to arise from excessive stimulation of dendrites, and in that of relay nucleus stimulation (King, Schricker and O'Leary 1953) from activation of cell somata. Yet both appear to have their origins in the superficial half of the cortex. This problem can only be settled by fractionation of the cortex by electrodes sufficiently stable to permit coincident recording of D.C. shift and the convulsoid transients.

SUMMARY

1. Cortical D.C. changes occur incident to stimulation of the mid-line thalamus of rabbit and cat.

2. At stimulating frequencies which elicit recruiting a negative D.C. shift ordinarily occurs in the rabbit. In the cat there is no shift or a minor positive one may occur.

3. In the rabbit with high frequency stimulation a negative D.C. shift results which may obtain an amplitude of 1.5 mV. and persist for several seconds into the post-stimulatory period. In the cat there is also a negative shift, but it is usually less manifest than the rabbit.

4. The D.C. shift with low frequency stimulation results from summation of after-effect. At high frequency stimulation the D.C. shift is accounted for by summation of transients as well as summation of after-effects and is regarded as a steady state of activity in dendrites.

5. Prolonged stimulation (10-15/sec.) may introduce other effects which occasion the return of the D.C. shift to the pre-stimulatory base line and post-stimulatory positivity.

6. The after-effect following the initial response of a recruiting series is associated with increased excitability. The negative D.C. shift following brief repetitive stimulation and the positive one following prolonged (10-15 sec.) stimulation are associated with decreased excitability for a test recruiting series.

7. Intense repetitive stimulation in the relay nuclei of the thalamus may occasion cortical paroxysm on a base line indicative of positive D.C. shift, whereas corresponding stimulation in the mid-line thalamus has been shown to relate to negative D.C. shift. At present no explanation can be offered for this difference.

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DIFFERENTIAL ELECTROENCEPHALOGRAPHIC RESPONSE TO CONDITIONED AUDITORY STIMULI IN AROUSAL FROM SLEEP [1]

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The work of French and Magoun and colleagues (1952, 1953) has shown the essential role of the brain stem reticular formation in EEG arousal. As an extralemniscal sensory system, it receives impulses via collaterals from the specific ascending sensory systems, and, as a diffuse activating system, causes the desynchronization of the electroencegralogram characteristic of the waking state. The question arises as to how the various afferent stimuli are differentiated so that indiscriminate arousal with every sensory input does not occur. That such discrimination does take place is suggested in our everyday experience by arousal from sleep to "important" sounds, and sleeping through "inconsequential" sounds despite their greater intensity. Further, Fischgold (Jasper 1957) and Lairy-Bounes and Fischgold (1953) have found that the EEG of a stuporous patient can desynchronize to the calling of the patient's name, whereas less significant auditory stimuli, and even pinching, leave the record unchanged.

The ability of cortical stimuli to cause diffuse activation via the reticular formation demonstrated by French, Hernández-Peón and Livingston (1955) suggests that discrimination can occur by interactions of specific and non-specific systems at loci more rostral than brain stem tegmentum and can govern the general activation by the reticular formation. On the other hand, evidence has been presented by Hernández-Peón and Scherrer (1955) indicating that evoked responses in cochlear nucleus are blocked by reticular influence in the process of habituation and that this blocking is differential, not occurring with novel stimuli. It may be presumed that, at least with simpler afferent stimuli, the discriminatory functions can be accomplished at fairly caudal levels in conjunction with brain stem reticulum.

Morrell and Jasper (1956) demonstrated cortical desynchronization as one of three types of EEG response occurring in sound-light conditioning and showed this to be a differential response in that it was absent when unreinforced stimuli were presented.

In a study not involving conditioning, but penetrating the phenomena of habituation, Sharpless and Jasper (1956) found differential arousal responses specific to quality, modality or pattern of the stimulus. These responses were of two types: a less discriminating tonic form which correlated with influence of lower levels of ascending reticular system; and a more differentiating phasic form correlating with function of higher (thalamic) levels of the unspecific and adjacent sensory systems.

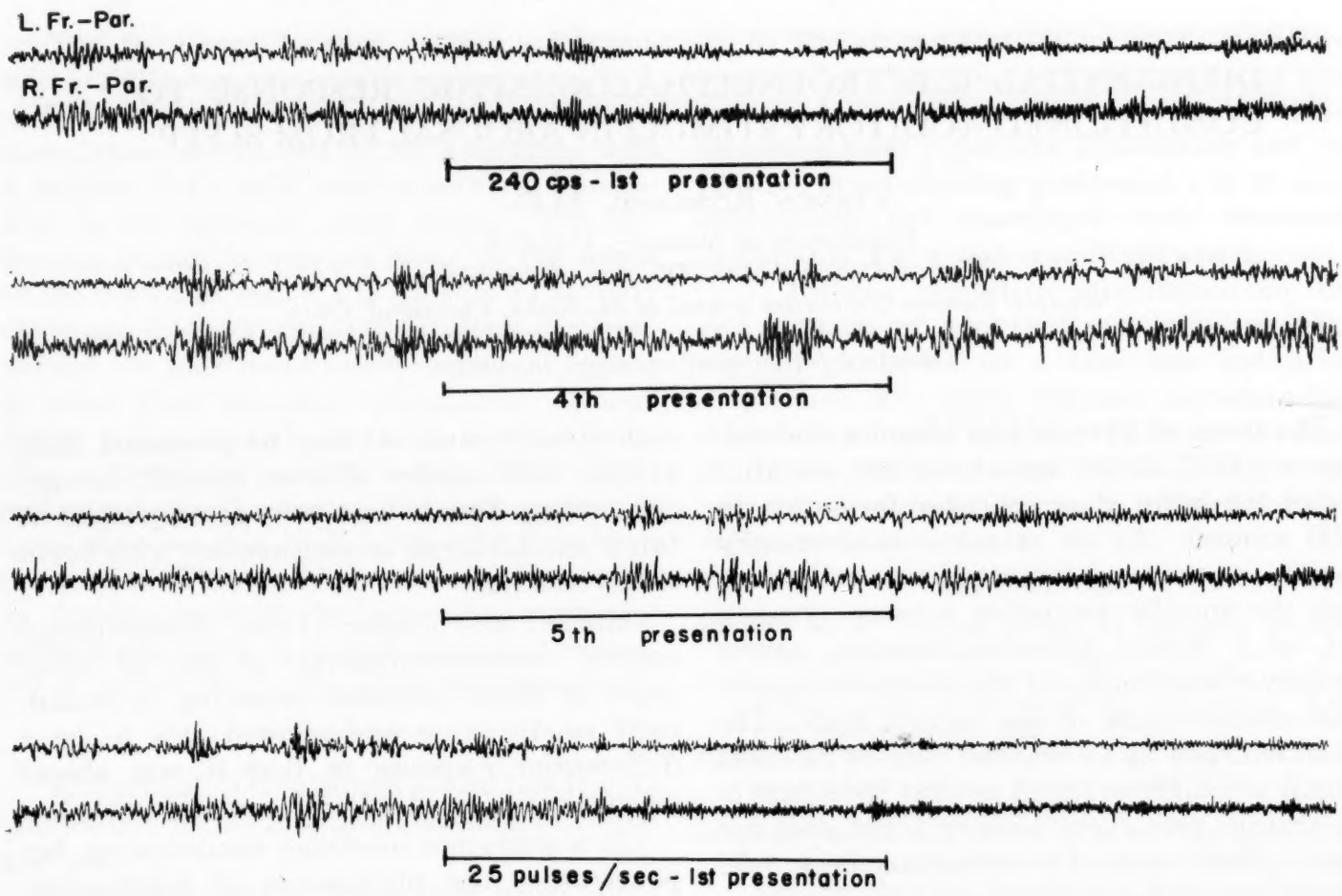
The purpose of the present study was to test the phenomenon of discriminated arousal from sleep utilizing affectively charged conditioning.

TECHNIQUE

Six cats with electrodes implanted principally on lateral and sigmoid gyri (one animal had deep implants), were classically conditioned while awake. This was accomplished within 10-15 trials, to a tone of 10 sec. duration (CS) by the presentation of a painful ½ sec. shock (US) delivered at the end of the tone, to the shaved skin under a permanent harness. The animals were further exposed to this conditioning 20-50 times. All testing was done "on extinction" during

1 Work done as part of a career-investigator grant of the National Institute of Mental Health.

DISCRIMINATION OF DIFFERING SOUNDS



sleep. Training and testing took place in the same laboratory area, which was in a room separate from that housing the home cages. Neutral tones were sometimes presented in the waking state for testing discrimination and at other times were withheld in order that the cat's first exposure to them would occur while it was asleep.

The cats were required to remain awake through the night preceding the day of testing by being placed in shallow water without opportunity to lie down. The next day, on being dried, fed, and placed in the darkened testing room, they remained curled up with eyes closed for several hours. Ambient noise could be minimized but not entirely eliminated since the animals were not in a soundproof testing room. However, with the above-described sleep-deprivation, the animals showed minimal or no behavioral or EEG arousal even to fairly intense extraneous but familiar sounds over which there was no experimental control, such as those of airplanes or water pipes.

Sounds were produced by a Tektronix Stimulator output (two stimulators in the case of tone patterns) amplified and delivered to a loudspeaker one foot from the cat's cage. Sound intensity was controlled by measuring, with a calibrated microphone and vacuum-tube voltmeter, the decibel level of tones used relative to an arbitrarily chosen 0-reference level. Neutral tones were always of intensities equal to and usually slightly greater than those of the conditioned tones. Frequencies used were from 25 to 1500 pulses per sec. Since the pulse generator produced square waves, the low frequencies represented rapidly repeated clicks, rather than the low tones of sine waves at those frequencies. The low frequencies were utilized to produce non-tonal sounds of marked qualitative difference from the pure tones of the higher frequencies.

The various auditory stimuli were repeated many times to eliminate novel stimulation as a factor in EEG arousal. They were presented at random intervals and in random order to eliminate monotony or periodicity as factors in adaptation. The intertrial interval varied from 2 to 20 min., depending on the sustained return of suitable EEG background. The animals were considered to have met criterion on the demonstration of 5 consecutive differential responses.

Ablations of auditory cortex were accomplished under direct visualization by use of electrocautery with needle penetrating to a depth of one centimeter. The location of cortical electrodes was verified by inspection at time of sacrifice and the deep placements (1 cat) were verified histologically.

RESULTS

In all of the 6 cats used it was found that differential behavioral response to sounds was attained and revealed in the waking state by obvious flinching, cringing, defecation, urination or cessation of eating or grooming on presentation of the conditioned stimulus, whereas no such behavior accompanied the neutral sound. When the animals were curled up with eyes closed in behavioral sleep, there was rarely any movement (usually seen only at the onset of testing) to suggest behavioral arousal to the conditioned stimulus, but the encephalogram demonstrated characteristic change from the synchronous pattern with spindles to low voltage fast activity. This change was not seen in relation to the neutral stimulus once the animal had "adapted it out". This process could be observed in its entirety if the animal was not exposed to neutral stimuli while awake.

The animals very readily showed differential EEG response to sounds of differing quality. Figure 1 demonstrates an animal negatively conditioned to 25 clicks per sec. (quality of a drum-roll). The first presentation of the neutral sound (a tone) which was given during sleep, was accompanied by transient and partial desynchronization. By the fourth presentation, however, the spindling

Fig. 1

Responses to neutral (240 c/sec.) and conditioned (25 pulses/sec.) stimuli with transient desynchronization to the first trial and subsequent adaptation (4th trial) and synchrony response (5th trial). Subsequent records show enhanced and maintained differential responses representative of the discriminations which were stable through the 30th trial.

continued throughout the stimulus (habituation or adaptation). When there was relatively little spindling in the background activity (5th trial), increased spindling developed with the neutral tone. This phenomenon was observed on many occasions and could even be utilized at times to induce a background record having more spindles. The first presentation of the conditioned stimulus in sleep is then seen, in the next record (fig. 1), to produce a sustained desynchronization. Responses to such first presentations of CS were often characterized by rather long latency (2-3 sec.) which, disappearing on subsequent trials, were replaced by more rapidly appearing and more sustained desynchronization. On later presentations of the same sounds (18th trial in fig. 1) one sees even greater differences demonstrated in the responses to CS as compared with those to the neutral sound. After the differential responses were demonstrated in this way, it was frequently observed that EEG desynchronization was unaccompanied by a behavioral manifestation of arousal, the cat remaining tightly curled with eyes closed. Occasionally an ear was cocked without other motor manifestations. The discriminated responses manifested in this way remained stable until extinction occurred gradually from the 30th to 50th trials. Extinction was characterized by longer latency in appearance and shorter

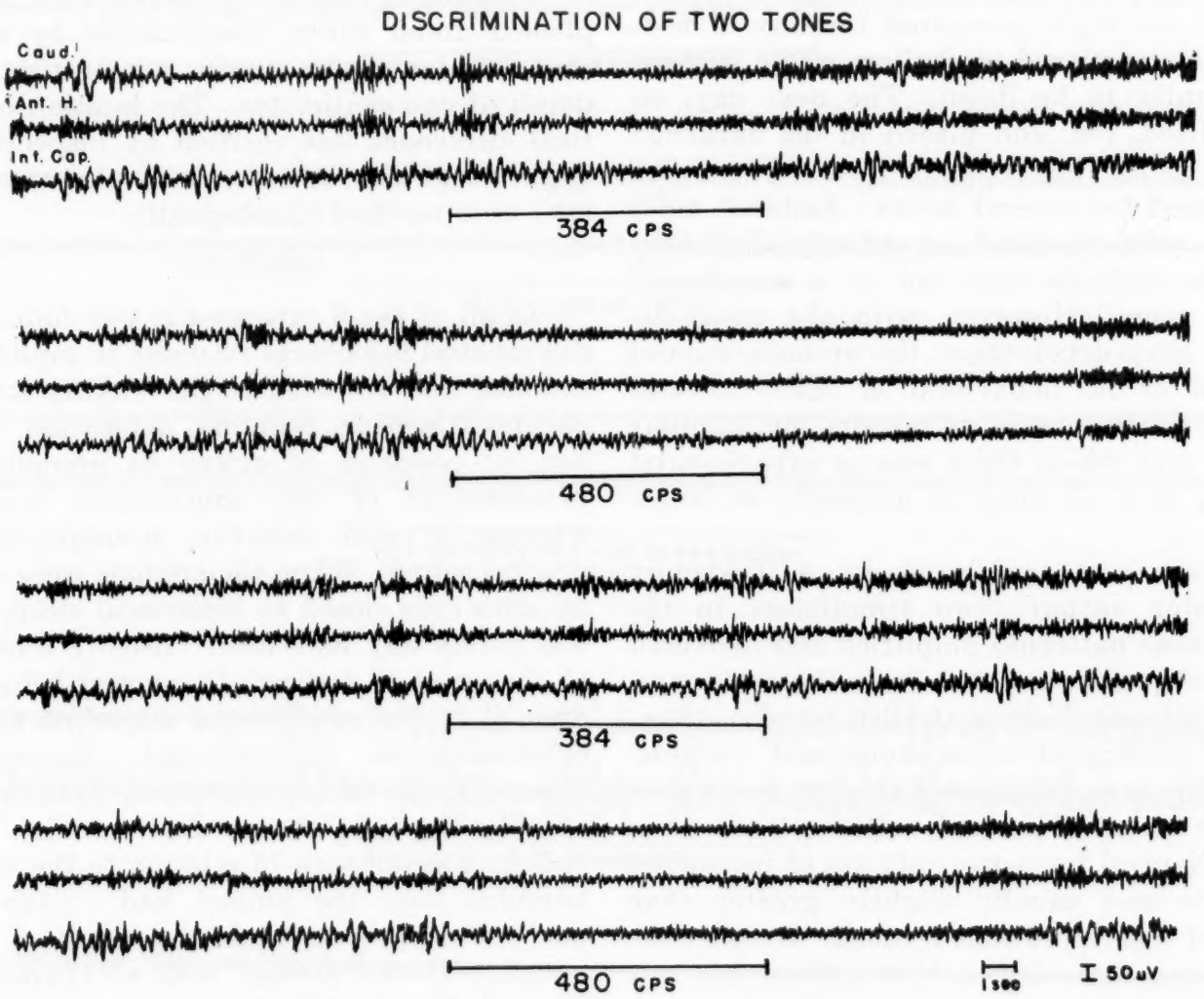


Fig. 2

Discrimination of differing tone frequencies rather than of differing sounds as shown in figure 1. First record shows early presentation of neutral stimulus, 384 c/sec., accompanied by transient desynchronization, disappearing on next trial of same tone (3rd record). Second and fourth records show the sustained desynchronization accompanying early and late trials of the CS (480 c/sec.). Leads are from caudate, anterior hypothalamus and border of internal capsule near reticular nucleus of thalamus.

duration of desynchronization. Early responses lasted up to 60 sec. or more and gradually shortened to a second or so before disappearing entirely, leaving a response of spindle-abeyance of 10-20 sec. duration (i.e. continuous inter-spindle background without desynchronization). This finally gave way to no alteration in spindle pattern during the 10 sec. of CS presentation, as shown in figure 3, first record.

again be elicited after the animal spontaneously awoke. Figure 3 illustrates this in the cat which was conditioned to a 480 cycle tone, with extinction to this shown in the first record. Shortly after this, the animal spontaneously roused and showed a desynchronized record that did not alter with presentation of a neutral tone one octave higher (960 c/sec.). However, the first return to the CS (480 c/sec.) after the animal awakened

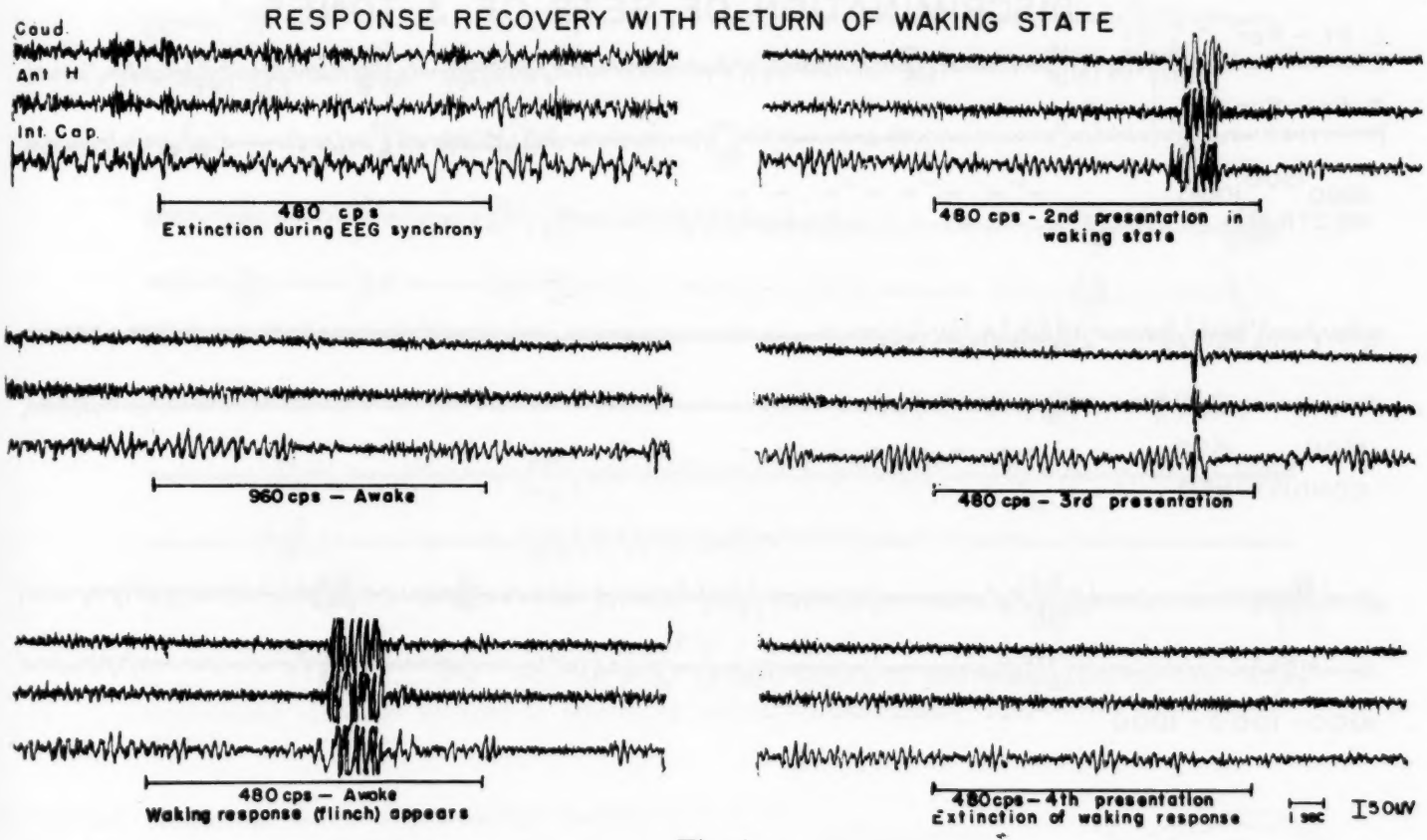


Fig. 3

Same cat as that from which records of figure 2 are taken. First record shows extinction to CS (480 c/sec.). Next record below is trial of neutral tone (960 c/sec.) after "spontaneous" arousal. Third record shows flinch indicated by movement artifact which on next three records disappears.

Discrimination of two tones, in contrast to sounds of differing quality, is not accomplished as readily, but has been achieved and carried to as small a frequency difference as that between 384 c/sec. and 480 c/sec. (fig. 2). This does not represent any attempt to reach the minimal interval for discrimination. Enhancement of spindle pattern with the neutral tone as illustrated in figure 1 is not observed in this presumably more critical type of discriminatory task.

After extinction in EEG response a behavioral response (cringing or flinching) could produced a flinch recorded as a movement artifact in the record. This rapidly extinguished by the 4th trial (fig. 3).

A more complex neutral stimulus consisting of two frequencies presented in the pattern illustrated in the first record of figure 4 was used in another cat for comparison with an inversion of the pattern utilizing the same frequencies and serving as the conditioned stimulus (2nd record fig. 4). In conditioning, the shock was delivered at the end of the 4th triplet. A reaction similar to that for discrimination of sounds and tones is seen, and

in this particular animal there are two changes in the record occurring during the stimulus. The first appears during the first half of the stimulus (2nd record of fig. 4) and is characterized by higher voltage slower activity replacing the spindles and itself then being replaced by the classical desynchronization pattern as the stimulus approaches its end.

This animal had previously been trained to discriminate the easier sets of tones shown in the 3rd and 4th records of figure 4, the 1500 c/sec. set being the conditioned stimulus. The illustrations shown were taken from trials of these, re-presented after the foregoing more complex patterns, but without further reinforcement. They illustrate a probable frequency dependence for the discrimination of the complex sets, and show the animal did not accomplish a pure pattern discrimination independent of frequency cues. But it is also seen that mixing the two frequencies in this way did not obscure their cue values.

In this same animal, presentations of just one of the four triplets constituting the entire conditioned stimulus (''¼ CS'' in fig. 5) produced only transient desynchronization. Two such triplets (3rd and 4th records) produced a more sustained abeyance of spindles and slight desynchronization. Three such triplets are then seen to produce the pattern nearly characteristic for the full four triplets of the entire CS but with full and sustained desynchronization occurring after a longer latency.

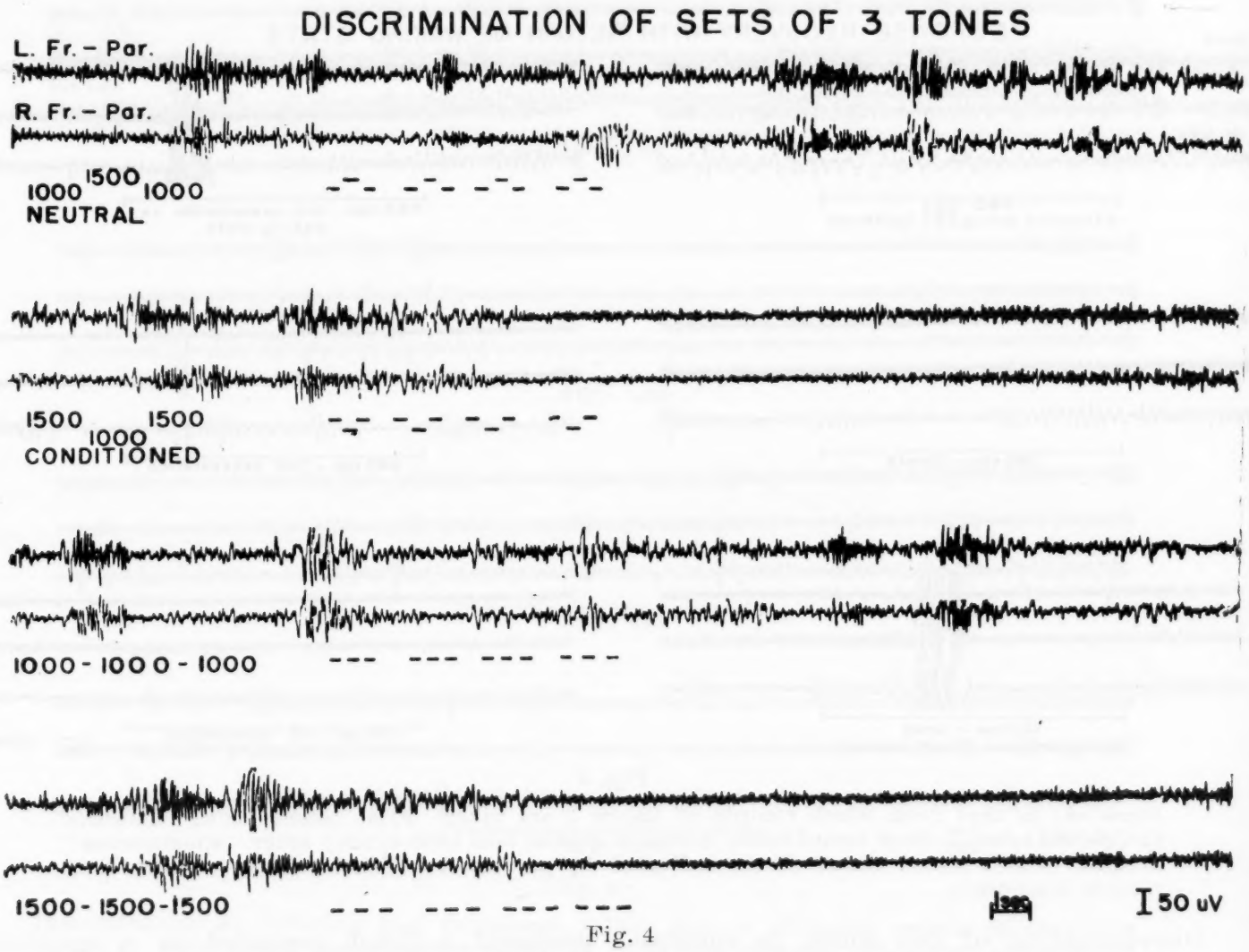


Fig. 4

Tone patterns involving frequencies indicated at left and distributed as shown by the dash lines over the course of 8-10 sec. For further explanations see text.

The problem of anatomical sites involved in these discriminations was approached by ablation of auditory and adjacent cortex in three pre-operatively trained and tested cats. One of these, without post-operative training or reinforcement, showed retention of dif-

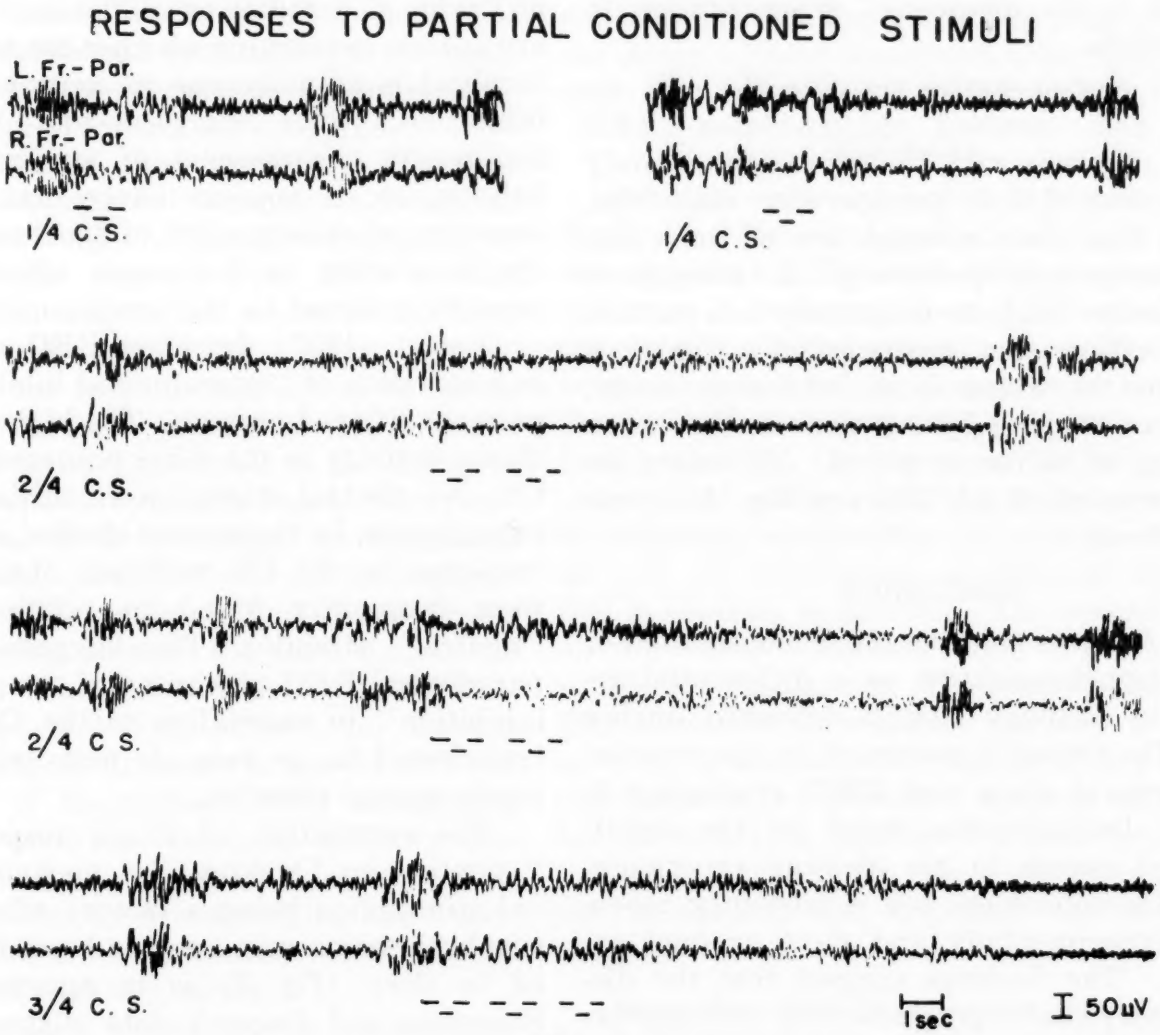


Fig. 5

Same cat as for figure 4. The fraction at left refers to the proportion of the full conditioned stimulus utilized in observing effect of numerically incomplete conditioned stimuli.

ferential response both in waking behavior (flinch) and in the EEG arousal response. The latter, although definite, disappeared within 5 trials and was stabilized only after subsequent reinforcement. The other two animals, also without post-operative reinforcement, showed similar definite but rapidly extinguishing discriminated arousal. They were not tested for waking response in view of the rapid extinction of the EEG response of the first animal, but their EEG responses proved to be no more durable. One of these post-ablation cats, after acquiring a discriminated arousal response to a new CS tone used only with post-operative training, showed a briefly restored response to its preoperative CS tone without that stimulus ever having been used in its post-operative training. This

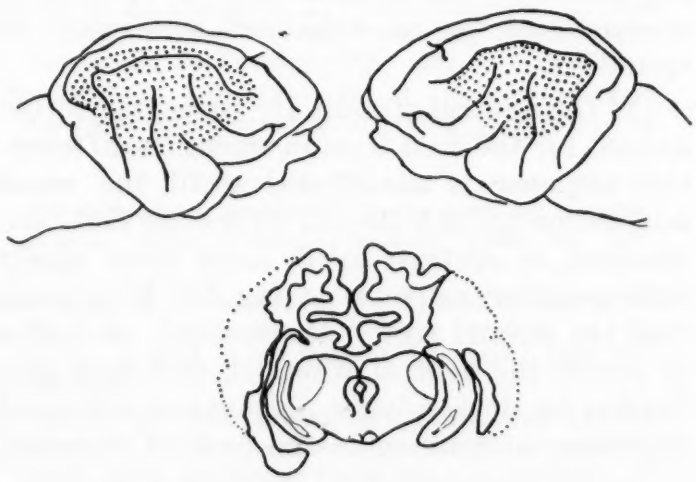


Fig. 6

Extent of greatest magnitude of cortical removal in the three cats studied after ablation.

occurred in the absence of generalization to other sounds.

With post-operative training the cats acquired and retained discriminated EEG arousal response with facility approximately equal to that of their pre-operative capacities. The cat that discriminated sets of tones lost this capacity post-operatively. An attempt to train another cat post-operatively to a pattern discrimination was unsuccessful. Figure 6 illustrates the widest extent of lesions made; the others varying by 1-3 mm. in the lesion periphery at different places. All lesions involved removal of AI, AII and Ep. AIII was not involved.

DISCUSSION

The findings confirm the demonstration of EEG desynchronization as a differential response to auditory stimuli delivered during sleep. The animal is presumed, in the presence of behavioral sleep and EEG synchrony to make a discrimination based on the significance of sounds in his training experience. These discriminations are consistently reproduced experimentally and show gradual extinction. The findings suggest that the discriminatory challenges presented, once mastered (i.e. criterion attained), do not require the presence of a desynchronized record (at least from the areas recorded) for, with the neutral tone, no such desynchronization occurs. On the contrary, the neutral tone is frequently accompanied by an enhanced synchrony or spindling.

If the neutral stimuli are presented to the animal for the first time in sleep, no differential response is manifested until the rapid adaptation to such stimuli leaves the EEG unchanged, in contrast to the much more slowly extinguishing response to the CS. It appears that the animal first ''adapts out'' or learns to ignore the neutral stimulus, and then goes further by developing a response of enhanced spindling in relation to the neutral stimulus.

If the discrimination demanded was more acute, as between two tones of small frequency difference, or more complex as with mixed frequencies in patterns, this enhancement of the synchronous record was not observed. The enhanced synchrony is perhaps a correlate of Pavlov's ''irradiating inhibition'' but there are no data concerning whether the mechanism involved is actually one of neurophysiologic inhibition. Since Sharpless and Jasper do not report enhancement of synchrony with habituation, it appears likely that the phenomenon of enhancement of synchrony develops in relation to the strong affective components involved in the conditioning process.

Jouvet (1957) describes EEG synchrony as a correlate of ''supraliminal inhibition'' in pain-conditioned animals. The higher voltage, slower activity in the EEG occurred with the CS. No neutral stimuli were utilized in his experiments. In the present studies, such EEG responses to the CS were not observed, but were frequently found in relation to the ''neutral'' stimulus. This suggests that the paradoxical EEG synchrony of ''supraliminal inhibition'' in association to the CS may be transferred to, or arise *de novo* with, a formerly neutral stimulus.

The restoration of flinch response with ''spontaneous'' waking (i.e. no known external stimulation being a factor) after the desynchronization response has been extinguished in sleep (fig. 3) is in agreement with Sharpless and Jasper's data suggesting that the potency of the non-specific activation from novel stimulation is the mechanism of response restoration rather than blocking of the inhibition (''disinhibition'' of Pavlov). Further weight is given in this direction in that general arousal, even in the probable absence of novel stimulation, occurred here and was followed by response recovery. The neutral tone given prior to the CS after the animal awoke was not a novel stimulus since it had been given many times during the sleeping state.

An additional experiment was performed in one cat which demonstrated that these arousal responses to sounds appearing in a context of silence could also be demonstrated in the reverse relation — of silence appearing in a context of sound. Thus, a cat was exposed to continuous 1/sec. clicks and trained to expect a shock at the end of 10 sec. of silence. This silence was as evocative of EEG arousal in the sleeping animal as the sound stimulus was for the other animals. Discrimination studies were not further developed in this

animal in relation to this except to show that extraneous noises and tones added to the background clicking were quickly "adapted out" or failed to produce arousal altogether.

Thus, although most experience is of the type in which external stimulation is added, there is good evidence in this experiment of the capacity to respond with EEG arousal when external stimulation is subtracted from the background.

At least the location and extent of cortex depicted in figure 5 (including AI, AII and Ep) appear to be dispensable to the differential EEG response to simple tones. More complex discrimination as tested by reciprocal three tone sets was not effectively demonstrated in the ablated animals and demonstrates for the sleeping animals the same limitations as shown by Diamond and Neff (1953), Butler, Diamond and Neff (1957), for waking animals. These findings are in accord with the conclusions of Galambos (1954) concerning the role of auditory cortex in auditory discriminations. It is found in this study that the EEG synchrony accompanying the "neutral" stimulus is also resistant to the described ablation of auditory cortex.

More accurate localization of mechanisms in these phenomena awaits further study. Sharpless and Jasper attributed more discriminatory functions to thalamic levels of the nonspecific reticular system. Applying their conclusions to the present studies suggests that the presence of synchrony response to neutral sounds in simple discrimination and its absence in complex discrimination is related to the degree of lower (tegmental) components of reticular influence. Thus, the greater the divergence in response between CS and neutral stimuli, the more caudal the level of reticular influence to be expected.

These studies demonstrate that, in the process of extinction, the behavioral response of opening the eyes and raising the head, in association with alerting or arousal, disappears within a few trials of the CS, long before full extinction of the desynchronization response. There may persist for some time movement of one or both ears, but this is unstable and shows extinction prior to that for the EEG response. Thus there is much evidence to indicate that EEG desynchronization can occur without associated behavioral arousal.

SUMMARY

Six cats with implanted electrodes, classically conditioned to paired sound and shock, demonstrated differential EEG desynchronization on a background of EEG synchrony associated with behavioral sleep. This phenomenon was used to demonstrate auditory discrimination in sleep of (1) sounds of differing quality, (2) tones of differing frequency, (3) mixtures of frequencies presented in reciprocal relationship (4) number of stimuli and (5) subtraction of external stimulation in contrast to addition. The neutral stimuli were seen to enhance EEG synchrony in simple discriminations. The conditioned EEG desynchronization response was seen to occur on many occasions in the absence of any motor manifestation of arousal. Removal of most, but not all cortex implicated in auditory function (AI, AII, and Ep) failed to alter simple discriminations, but impaired the complex ones.

The author would like to express appreciation to Dr. H. W. Magoun for use of laboratory facilities at the U.C.L.A. Medical Centre and to Dr. Carlo Terzuolo for collaboration in the initiation of these studies.

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ELECTROGRAPHIC ACTIVITY OF THE MESENCEPHALIC RETICULAR FORMATION DURING CONDITIONING IN THE CAT [1]

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INTRODUCTION

The results obtained in clinical and experimental electroencephalography by different conditioning procedures were reviewed by H. Gastaut in November, 1955, at the "Colloque de Marseille", which was devoted to the problem of electrical activity in the brain in relation with psychological phenomena.

At this meeting one of us (Yoshii) showed that the reticular formation of the brain stem plays an important role in the establishment of a positive conditioned reflex (defensive or salivary reflex). These results were in accord with the observations presented at the same meeting by Jouvet and Hernández-Peón (1955).

Morrell and Jasper (1956) when using intermittent photic stimulation as the unconditioned stimulus, observed peculiar conditioned responses, which can be characterized as follows:

(1) the conditioned electroencephalographic response appears at the beginning in the form of a generalized "desynchronization";

(2) later this "desynchronization" becomes localized to the area of the visual cortex;

(3) in between these two stages during the presentation of the conditioned stimulus (a continuous sound) a repetitive response of specific frequency is observed, i.e. a rhythm is recorded in the visual cortex which tends to follow the frequency of the light flashes used as the unconditioned stimulus.

We have been particularly interested in this latter observation and we asked ourselves whether it may not be possible to record these repetitive discharges which follow the frequency of the conditioned light flashes, in subcortical structures, particularly in the reticular formation of the brain stem.

TECHNIQUE

The purpose of this investigation was to study in the cat the electrographic changes induced in the cortex, thalamus and in the reticular formation of the mesencephalon during conditioning. Rhythmic intermittent photic stimulation was used as the unconditioned stimulus and a continuous sound as the conditioned stimulus.

In the four animals which were investigated the experimental procedure was identical: the animals were operated under Nembutal anaesthesia. The cortical electrodes were implanted in the bone in symmetrical positions over the frontal, auditory and visual cortices. Cement was used to hold the electrodes in place. The deep electrodes were introduced with the aid of a stereotaxic apparatus. In order to be able to use bipolar recordings paired electrodes were inserted into subcortical structures. The distance between the tips of these electrode pairs measured 1 to 2 mm. These subcortical electrodes were located in the nucleus ventralis anterior of the thalamus, the centre median of Luys and in the mesencephalic reticular formation.

After the third post-operative day the animal was placed in a calm and dark experimental room. During experimentation the animal was immobilized in a hammock. Usually the animals became easily accustomed to the experimental conditions. The experimenter and the recording equipment were placed in an adjacent room. Conditioning

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[1] This article was translated from the original French version on request of the author.

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procedures were carried out every day during a period of one to two months. The duration of the daily conditioning sessions did not exceed one hour. The experiment was interrupted as soon as the animal became agitated.

Intermittent photic stimulation was delivered without any disturbance by sound stimulation of 5 sec. duration which was started at the third second of the sound stimulus. The interval between succeeding paired stimulations was varied continuously, but was at the average of about 20-25 sec.

In all experiments anatomical controls confirmed the correct position of the electrodes

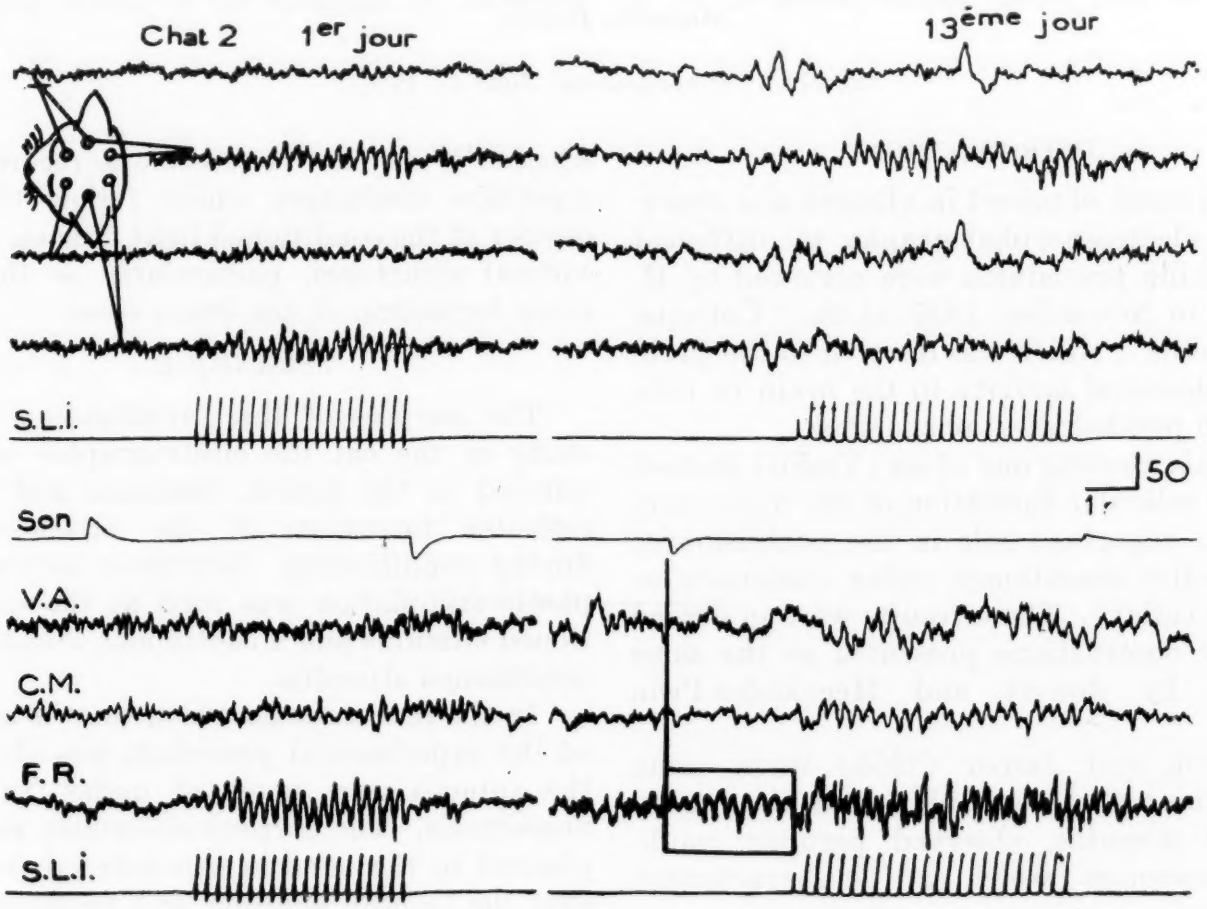

Fig. 1

Cat No. 2. The first four lines record the cortical activity in fronto-temporal and temporo-occipital regions. The next two lines are records of the unconditioned stimuli (rhythmic light flashes, S.L. i.) and of the conditioned stimulus (continuous sound, Son). The next three lines are records from the ventralis anterior nucleus of the thalamus (VA), the centre median (CM) and finally of the mesencephalic reticular formation (FR). The last tracing (S.L.i.) again records the photic flashes.
On the 1st day of the experimental series, the sound (conditioned stimulus) is still without effect and one observes the unconditioned response in the form of driving of the occipital and reticular activity at a frequency of the stimulating light flashes.
On the 13th day the sound produces the immediate appearance of a clear conditioned response in the form of a rhythm at the same frequency as the rhythmic light flashes. This response is recorded in the reticular formation.

with the "Epiphote" apparatus placed in front of the eyes of the animal at a distance of 40 cm. The conditioned sound stimulus of small intensity was delivered at a constant pitch by a "Sonoclat" apparatus.

The two stimuli were always coupled, the conditioned sound stimulus preceding and overlapping the unconditioned light stimulus. In almost all experiments a sound of 7 sec. duration was followed by a train of photic in the nuclear structures of the mesencephalon and diencephalon.

RESULTS

In the four animals used the daily repetition of the coupled sound and light stimulations produced changes in the electroencephalographic tracings. It is difficult to describe these modifications in all their fine nuances, especially since they appear very progres-

sively. Nevertheless these changes were quite evident when comparing tracings taken on succeeding days.

The successive changes of the electroencephalogram before conditioning, during the establishment of a conditioned response and finally during the onset of signs of an experimental neurosis can schematically be described as follows:

(I) *Before appearance of conditioning* the electroencephalographic records showed the following characteristics: (*a*) the resting cortical record was made up of rapid rhythms at 15 to 20 c/sec. of rather low amplitude (20-30 μV.). The record from the cortical regions was of the same type with some slower components (6-8 and 12 c/sec.). These rhythms of variable frequency alternated or became associated with each other continuously and it was impossible to observe a burst of waves with a stable frequency. Finally no synchrony between waves recorded in the cortex and those recorded in subcortical structures could be seen.

(*b*) The presentation of the unconditioned stimulus (intermittent photic stimulation for 5 sec.) evoked a driving at the specific frequency in most of the recorded areas. This driving was constant and no habituation developed. It reached its maximum amplitude (40-60 μV.) in the occipital regions and in the reticular formation of the brain stem (fig. 1). It was of somewhat lesser amplitude in the centre median of Luys. It was inconstant and weak in the nucleus ventralis anterior of the thalamus. In the frontotemporal region it was rarely seen (about one out of ten times) and was always of very low amplitude. From the morphological point of view the driven responses had the classical aspect of rhythmical spikes. However, on some occasions they assumed the aspect of a spike and wave rhythm.

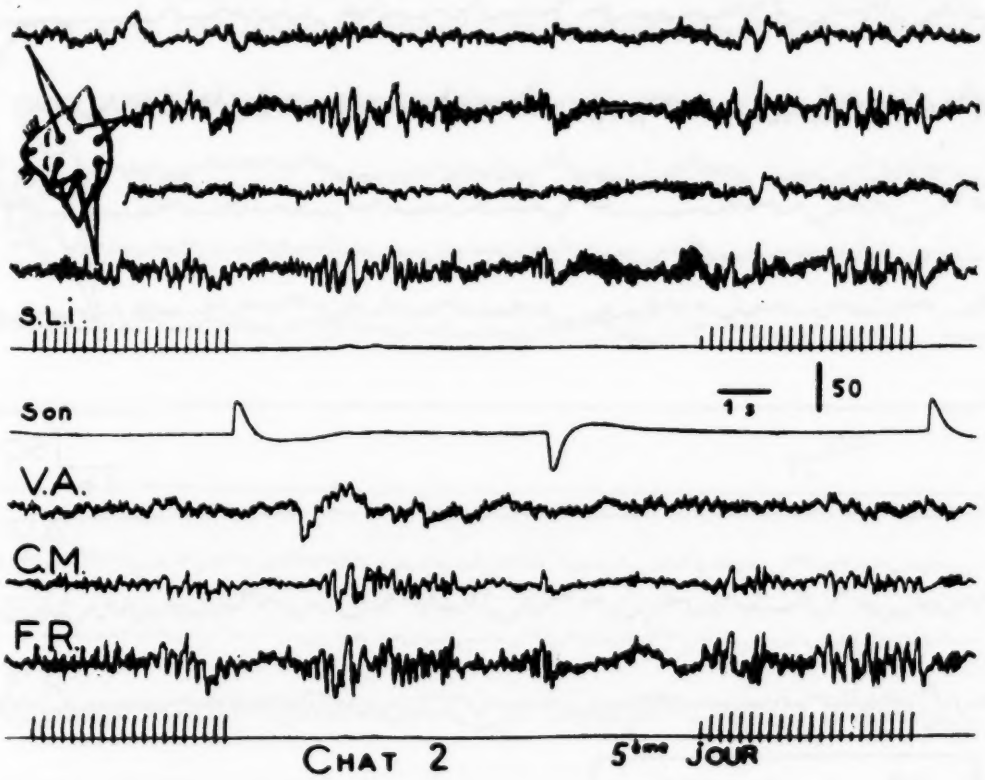

Fig. 2

Cat No. 2. Two phenomena appear from the 1st day on and here illustrated is a record taken on the 5th day of the experimental series.
(1) Between the end of the combined sound and intermittent photic stimulations and the beginning of the next sound stimulation higher voltage bursts appear in the resting record of the activity of the reticular formation, the centre median of Luys and of the temporo-occipital regions. Note the identical aspect of the bursts recorded in these different structures (''reticulo-occipital tuning'').
(2) As soon as the sound stimulus is applied desynchronization appears, characterized by a rapid rhythm of low amplitude (same record).

The driving usually ceased with the last stimulating flash, but sometimes it was seen to persist in the form of a short afterdischarge of not longer than one second duration which appeared in the occipital region and in the reticular formation.

(*c*) The conditioned stimulus (weak sound) produced an electroencephalographic reaction which showed rapid habituation. The evoked potential recorded from the auditory cortex (''on-effect'') and the consecutive desynchronization which were observed initially disappeared rapidly on the first day (fig. 1) and afterwards during the next two days the sound acted like any indifferent stimulus. Only on the fourth day the sound stimulus, always followed by the unconditioned light stimulus, became able to acquire the properties of a conditioned stimulus, as will be discussed presently.

(II) *Electrographic changes accompanying conditioning.* The repetition of the combined stimuli progressively produced marked changes in the records. The modifications appearing during presentation of the unconditioned and conditioned stimuli and during the intervals will be successively analyzed.

(*a*) Though the phenomena, to be described here, are not related to conditioning itself the changes of the response to repeated application of the unconditioned photic stimulus seemed to us to merit interest. Our attention was focussed especially on three phenomena which appeared after two days of experimentation:

(1) the driving at the specific frequency tended progressively to irradiate into the centre median of Luys, into the nucleus ventralis anterior of the thalamus and even to the fronto-temporal cortex. This is to say that

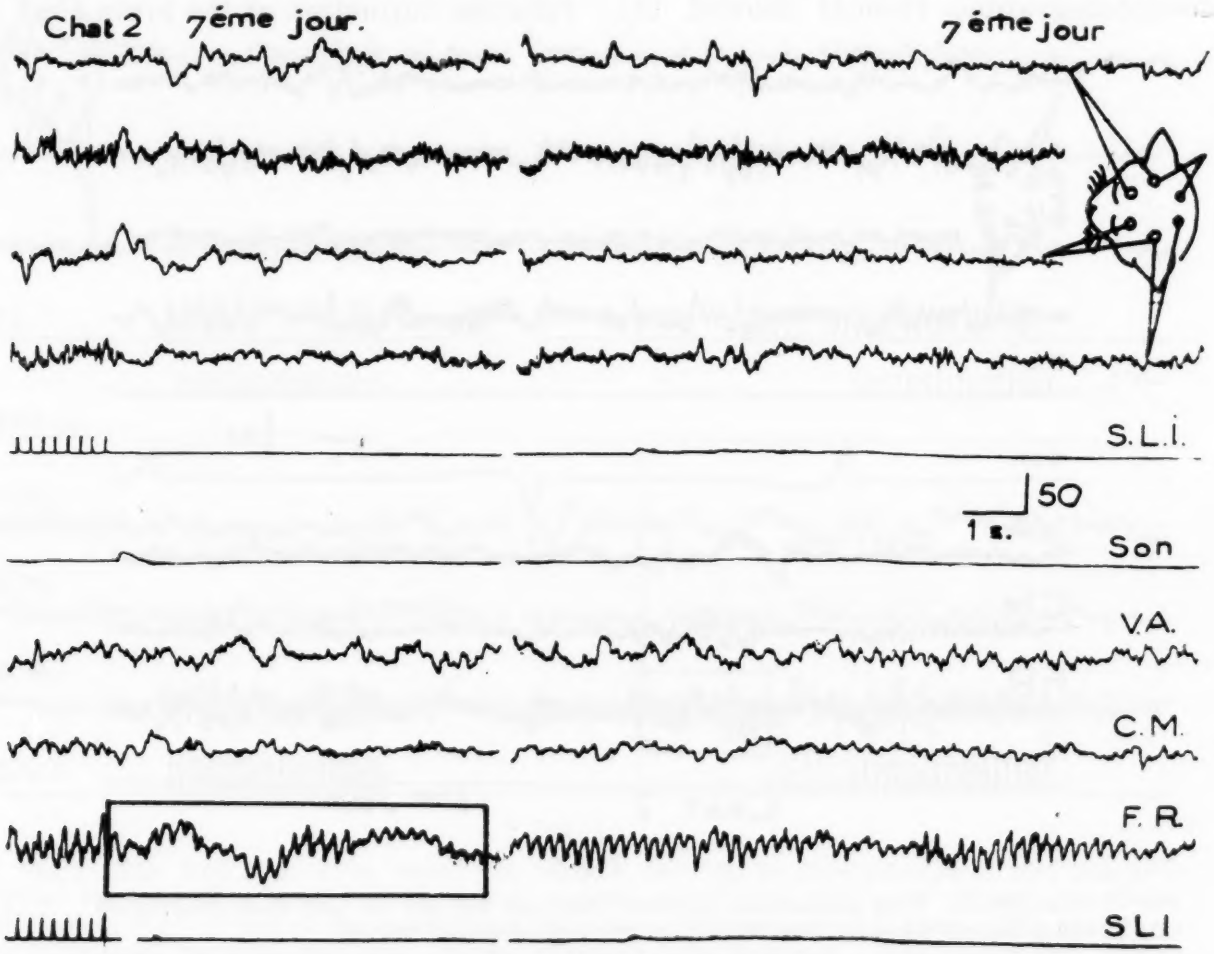

Fig. 3

Cat No. 2. Appearance on the 7th day of a spontaneous rhythm which in this case followed faithfully the frequency of the intermittent photic stimulation. This rhythm appeared:
(1) On the left side in the form of a reticular afterdischarge (FR) which persists for a long time after the unconditioned response;
(2) On the right side in the form of an independent rhythm appearing in fusiform bursts (same derivations).

the driving became more constant and of higher amplitude in all the structures where previously it had been seen only rarely and if at all at a low amplitude;

(2) the driving response lost its characteristic aspect of rhythmical spikes and more often assumed the form of a spike and wave rhythm;

(3) the "after-discharges" (this phenomenon was particularly clear in cat no. 2 which was stimulated at a frequency of 10 light flashes per second) became clearly more conspicuous (fig. 3 and 7). They occurred almost constantly and were now of long duration, measuring up to 10 and 20 sec. They predominated clearly in the reticular formation and in the centre median of Luys. They were also present though less marked in the temporo-occipital regions.

(*b*) The conditioned stimulus now became associated with clear electrographic changes: the evoked potentials and desynchronization (fig. 2) which had disappeared on the first day under the influence of habituation reappeared in all leads on the fourth day in response to the conditioning procedure. Only later from the 6th to the 8th day the desynchronization response was progressively replaced by the repetitive discharges described by Morrell and Jasper (1956), the frequency of which became more and more identical to that of the photic stimuli (fig. 1, 5 and 6).

As we anticipated these conditioned repetitive discharges were earlier in onset, higher in amplitude and more constant in subcortical structures, especially in the mesencephalic reticular formation. Finally, mention should be made of muscle potential artefacts, which occurred in temporo-occipital regions when the sound stimulus was presented (fig. 5 and 7). We paid special attention to this phenomenon since it was the electrographic expression of a state of muscular tension conditioned by the sound.

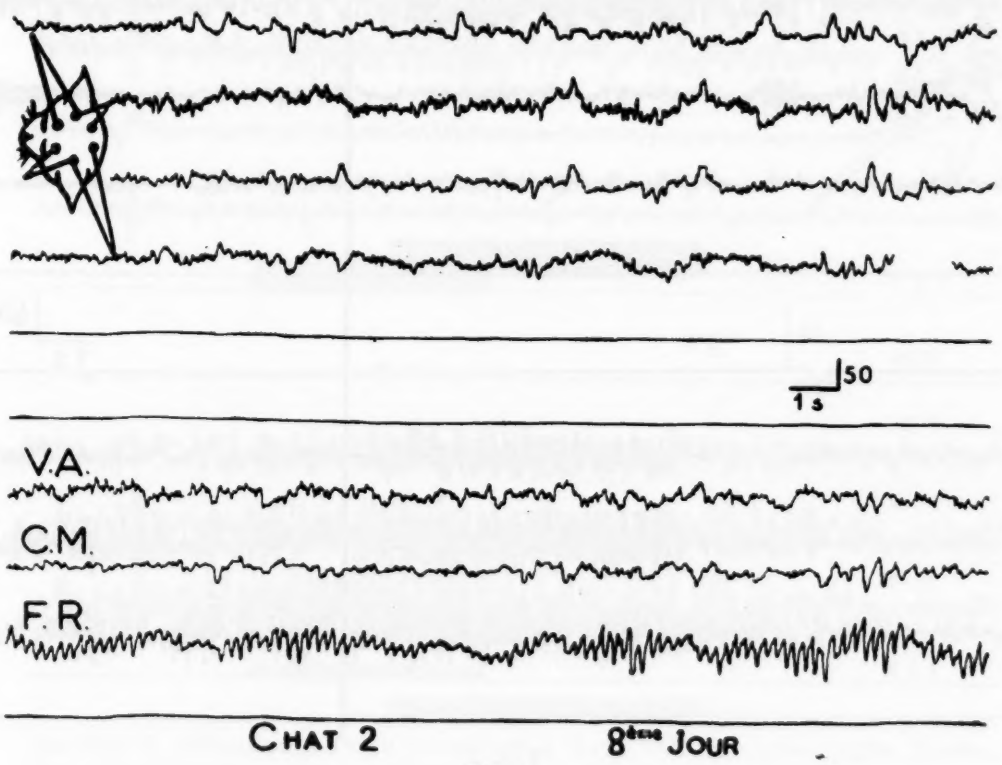

Fig. 4

Cat No. 2. Tracing taken on the following day shows the appearance of the spontaneous rhythm before any stimulation is carried out. This rhythm appears from the very beginning of the record (same derivations).

(*c*) During the intervals between the stimulations the resting pattern was also modified in the conditioning experiments. We paid particular attention to this phenomenon which so far has been studied only very little. In cat no. 2 the tracings from the cortex and those from the subcortical structures recorded during the first few days were clearly different from each other, yet towards the fifth day, there appeared an evident relationship be-

tween the electrical activity of the occipital cortex and that of the reticular formation. The relationships of phase, form and amplitude between the bursts and other electrographic elements of the tracings recorded in these two locations became increasingly more marked until, on certain occasions, they almost reached identity (fig. 2).

But the most remarkable phenomenon seen in three animals was the appearance of repetitive discharges, not only during the duration of the conditioned stimulus but also at other moments, when they appeared in the form of spontaneous bursts of more or less prolonged duration ranging between a few seconds and almost a minute. These bursts were made up of high amplitude regular waves of a frequency identical to that of the light flashes. These appeared progressively between the sixth and eight day and were preceded by a period of adjustment during which these bursts were of short duration, of low amplitude, and intermingled with rhythms of various frequencies, showing a repetition rate more or less close to that of the intermittent photic flashes.

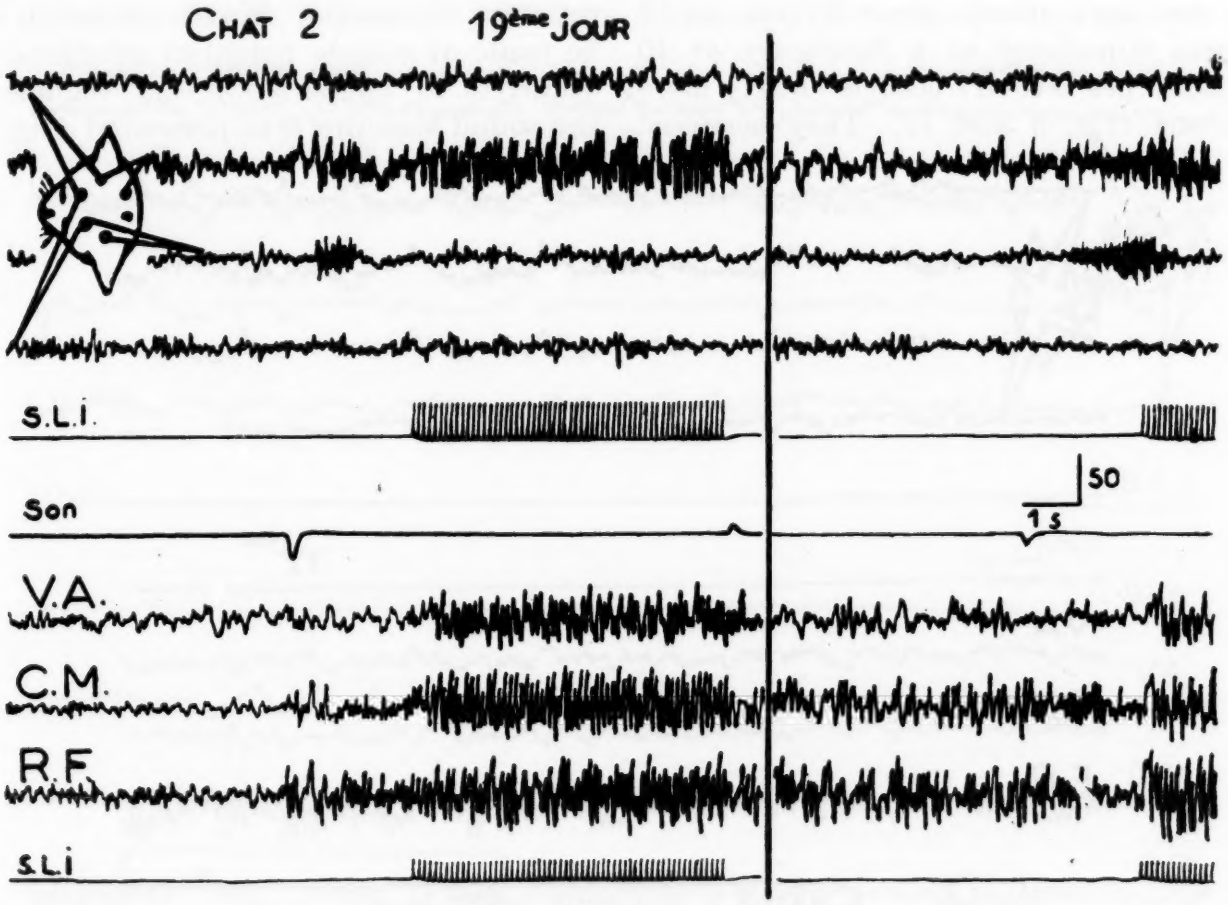

Fig. 5

Cat No. 2. Stimulated for three days with a frequency of 10 light flashes per sec. On the left is shown that as soon as the sound stimulus is applied the rhythms are markedly changed: in the reticular formation (RF), in the centre median of Luys (CM) and perhaps also in the temporo-occipital regions on the right side there appears a repetitive response which, though less high in voltage, is similar to the record taken during intermittent photic stimulation. On the right side are shown the 10 c/sec. rhythms which predominate in subcortical structures in the form of amplitude bursts.
Note also in the two fragments of the records that muscle potentials appear in fronto-temporal regions on the left side as soon as the sound stimulus is applied.
Note that the cortical derivations in this figure are a little modified. This was necessary because of deterioration of the left occipital electrode which was then no longer used. The 4th record in this figure is a bifrontal one.

These bursts were almost exclusively recorded from the mesencephalic reticular formation (fig. 3, 4, 8 and 9) and less constantly from the region of the centre median of Luys. Exceptionally they were also found in the occipital cortex, where they were concomitant to those recorded from the brain stem. This very peculiar rhythm following

the frequency of the light flashes (5 c/sec. for cats no. 2 and 4; 4 c/sec. for cat no. 3) appeared as soon as the animals were placed in the habitual experimental situation, i.e. when they were fixed in their hammock and placed in a darkened Faraday cage. In one case the recording conditions were deliberately changed. Thus cat number 2 was not placed into its habitual hammock, but put into a neutral place which was well illuminated. Under those conditions the 5 per sec. rhythm disappeared and reappeared progressively when the animal was transferred into its hammock and into its habitual experimental room.

In the same animal the frequency of the photic stimulation was then changed to 10 flashes per sec. After one day only there appeared in the reticular formation and in the centre median of Luys numerous afterdischarges and a spontaneous 10 c/sec. rhythms in a somewhat sketchy form which began to compete with the 5 c/sec. rhythm. Some days later the 10 c/sec. rhythm in the form of high voltage bursts became predominant in these subcortical structures (fig. 5 and 6).

Although these repetitive bursts disappeared in one case when the animal was placed outside its habitual experimental surroundings, they nevertheless reacted in quite a variable way to novel stimuli: they were blocked only inconstantly when various noises were presented (fig. 9) and their disappearance as well as their appearance did not seem to follow any precise rule nor to correspond to any modification in the external behavior of the cat.

(III) *Stage of experimental neurosis.* The behavior of the animal during these experiments varied from one individual to the other and the stage called "experimental neurosis" (a term here used in its broadest implications) was only observed in two animals.

Two cats were sacrificed early before any experimental neurosis could develop. The first of these two animals developed very rapidly, from the third day on, a tendency to somnolence with onset of slow waves and spindles (cat no. 1). This somnolence became progressively more accentuated and no conditioned response could be obtained. After sacrifice anatomical examination showed a left sided

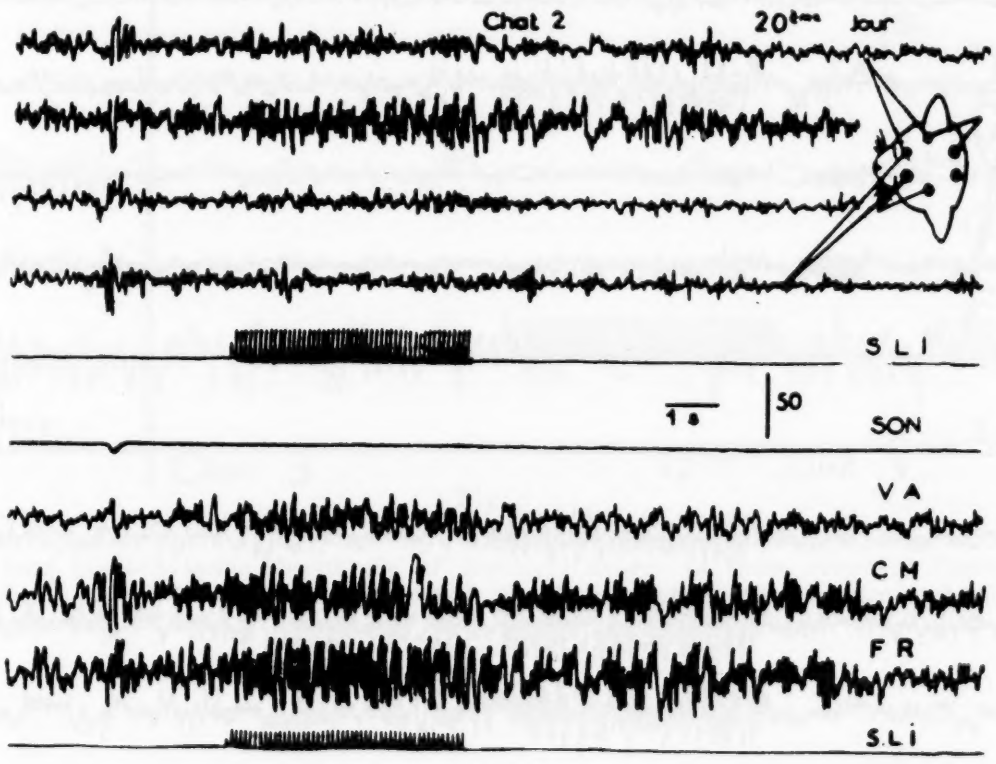

Fig. 6

Cat No. 2. Stimulated for a period of 4 days with 10 c/sec. light flashes. The presentation of the conditioned sound stimulus provokes the appearance of an evoked potential and modifies the preexisting rhythms. After the end of the unconditioned rhythmic light stimulus the 10 c/sec. high amplitude rhythms predominate in the reticular formation (FR), the centre median (CM) and less clearly in the right temporo-occipital regions (same derivations as in fig. 5).

cortical abscess. Cat no. 3 was sacrificed after 15 conditioning days because of the contamination of the records with artefacts originating from deteriorated deep electrodes.

Cat no. 4 had every day much difficulty to adapt to the experimental condition. The animal became very agitated as soon as it was placed into its hammock. It calmed down after about 40 to 50 repetitions of the coupled stimuli. This allowed to obtain conditioned repetitive responses after 6 to 7 days. After 15 days the animal became more agitated and also quite fearful, as evidenced by reactions of escape and recording became very difficult.

Cat no. 2 could be observed for more than 3 months. It showed conditioned and spontaneous repetitive discharges successively for frequencies of 5 and then 10 c/sec. After one and a half months the behavior of the animal changed and was characterized by alternations of periods of agitation and somnolence. The conditioned responses disappeared progressively and the application of the photic stimulus produced electrographic reactions of variable character which can be classified into three types:

(1) Type number 1 was characterized by a normal resting record and by a normal driving response to intermittent photic stimulation in subcortical and occipital regions (fig. 10).

(2) Type 2 appeared during the episode of somnolence during which the record contained spindles and numerous slow waves, whereas all reactions to the photic stimuli had disappeared or were considerably attenuated in records from all regions (fig. 11).

(3) Type 3, which in contradistinction to the previous type one may be tempted to qualify as the expression of a state of hyperexcitability, was characterized by a very rapid background activity and especially by a very peculiar response to photic stimulation consisting of rapid activity with harmonic frequencies recorded from both the reticular formation and the occipital cortex. The driving was also quite pronounced in the fronto-

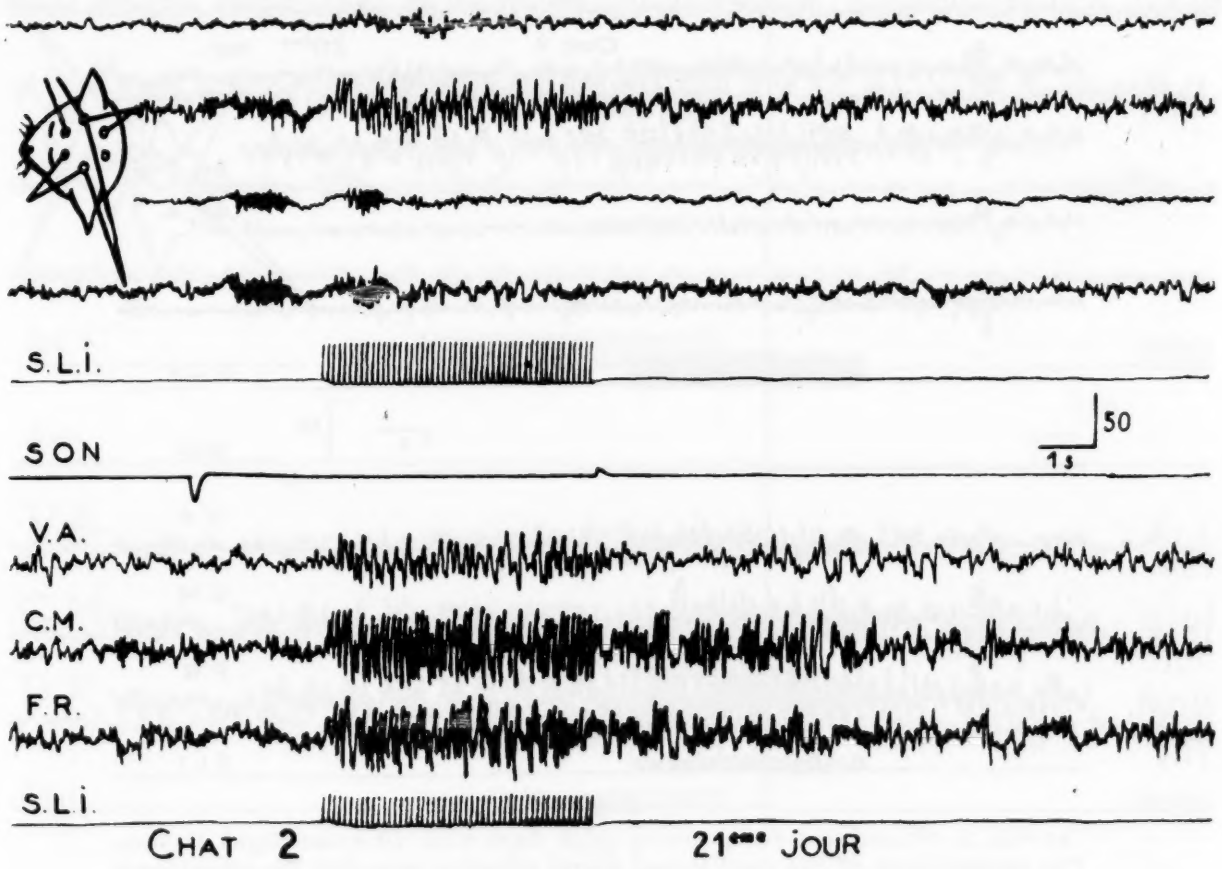

Fig. 7

Cat No. 2. Stimulated for a period of 5 days with 10 c/sec. light flashes.
(1) The sound stimulus provokes the appearance of muscle potentials recorded with the cortical electrodes.
(2) Persistence of high amplitude rhythms approximately at 10 c/sec. after the arrest of light stimulation (the 4th tracing is a bitemporal record).

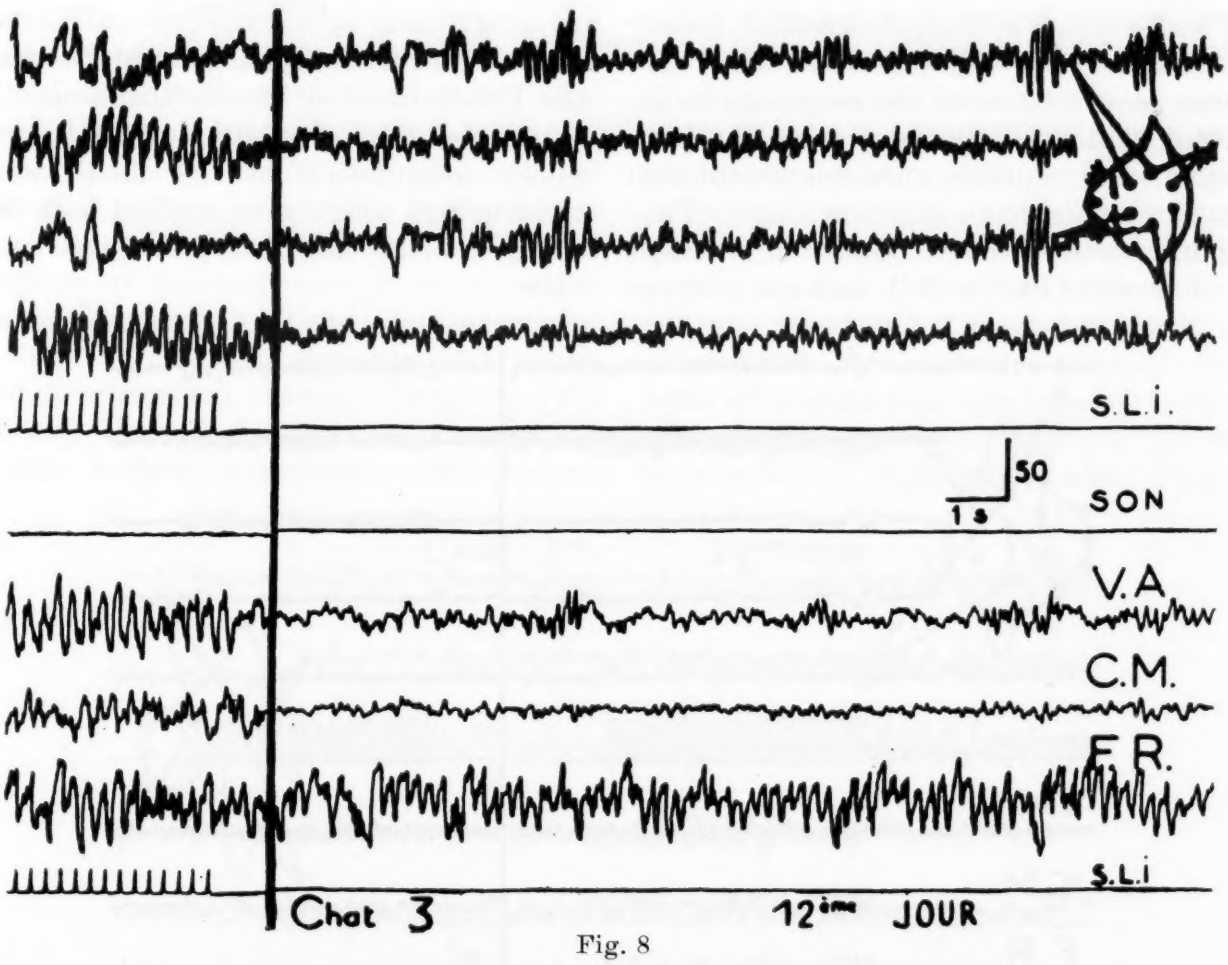

Fig. 8

Cat No. 3. Appearance of hypersynchrony strictly localized to the reticular formation in the form of long monorhythmic discharges of identical aspect to those recorded during intermittent photic stimulation. The frequency of these discharges becomes more and more close to that of the stimulating light flashes.

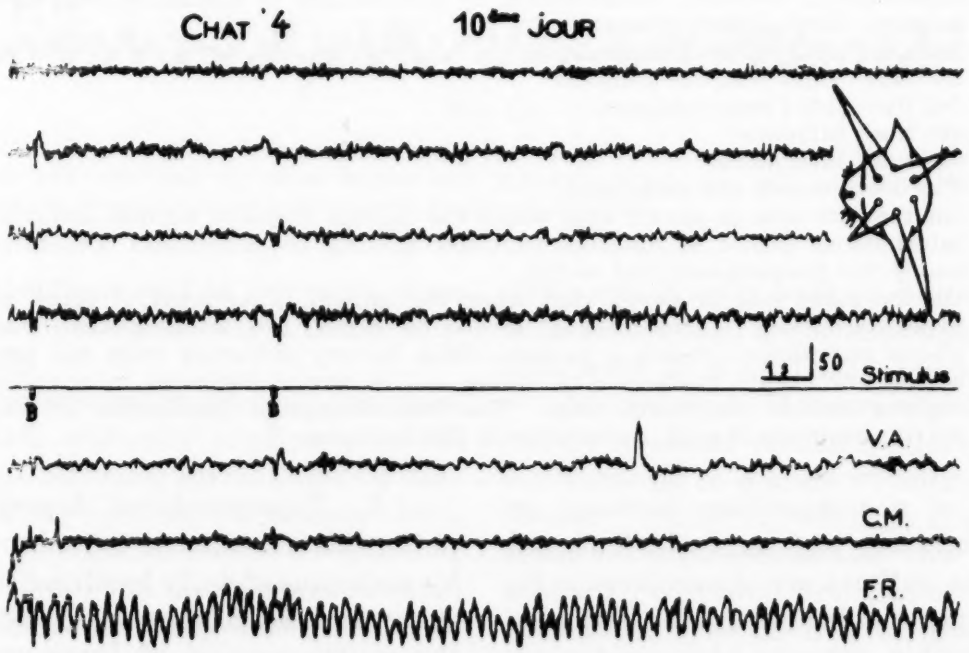

Fig. 9

Cat No. 4. Same phenomena as those described for cat no. 3 in figure 8.

temporal regions where it was barely noticeable during the normal state (fig. 10).

These peculiarities of the responses to intermittent photic stimulation during the stage of experimental neurosis were so clearcut that it seemed justifiable to mention them. They correspond without any doubt to variable states of cerebral excitability and are perhaps

DISCUSSION

I — Electroencephalographic Responses to the Unconditioned Photic Stimulus.

In the four animals studied intermittent photic stimulation evoked modifications of the tracings which were studied both from the topographical and morphological point of view.

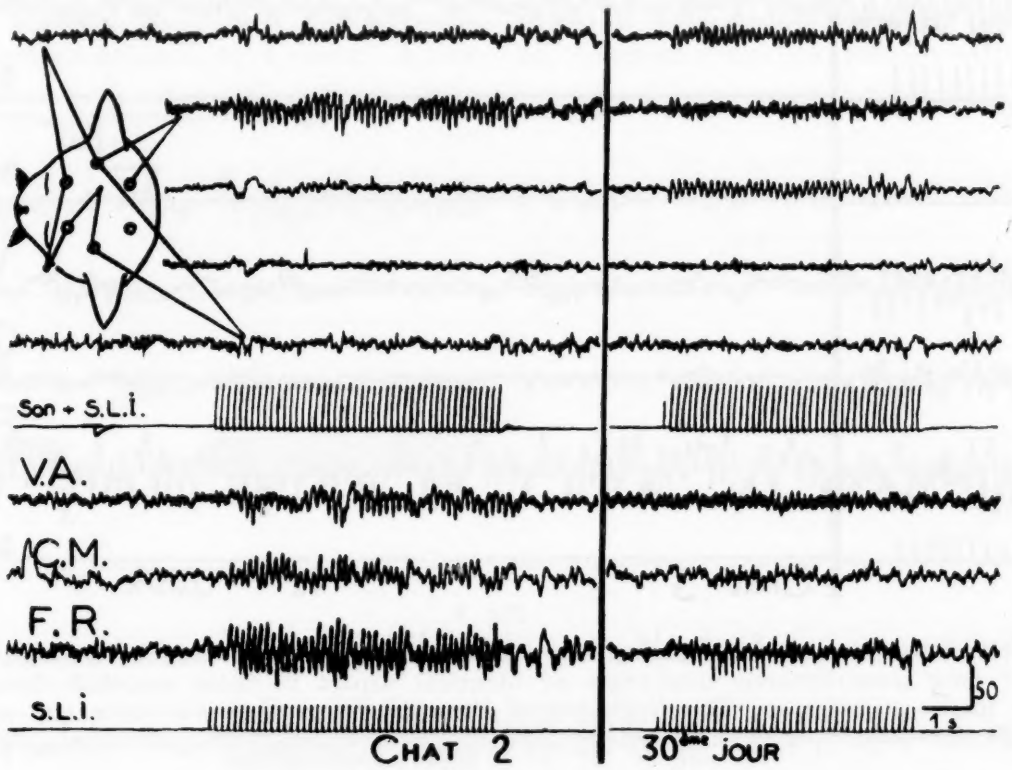

Fig. 10

Cat No. 2. Thirtieth day of the experimental procedure. State of so-called experimental neurosis, characterized by alternations of excitation and somnolence. Cortical derivations:
1st line: right fronto-temporal
2nd line: right temporo-occipital
3rd line: left fronto-temporal
4th line: bifrontal
5th line: bitemporal
The deep records are unchanged.
On the left side is shown that while the animal displays normal behavior intermittent photic stimulation provokes driving in subcortical structures and in the temporo-occipital cortex.
On the right side is shown that when the animal is agitated (''stage of hyperexcitability'') the resting record is rapid, low in amplitude and photic stimulation evokes a pattern which is very different from the preceding one: rapid rhythms with spikes and harmonic responses in occipital regions and in the brain stem. The fronto-temporal irradiation of the driving response is quite remarkable in this instance.

the expression of a competition between excitatory and inhibitory processes which according to numerous authors are characteristic for the state of experimental neurosis. The electroencephalographic aspects of neurotic animals were previously discussed by one of us (Yoshii 1951, 1955).

(A) *Topographical Aspects.* The evoked potentials in response to each photic flash were by no means strictly localized to specific visual structures, since they were also recorded from the centre median of Luys and from the reticular formation of the mesencephalon and even in the nucleus ventralis anterior of the

thalamus. To our knowledge these facts had not been systematically studied in the unanaesthetized animal up to 1955. Since Gastaut and Hunter (1950) had stated that in acute preparations under the influence of anaesthetic agents (Nembutal, Pentothal or curare), the subcortical and cortical frontal irradiations of the responses to photic stimulation is favoured by Cardiazol injections, some observations were done in the anaesthetized or curarized animal. Then, in 1955 Ingvar and Hunter showed that unanaesthetized cats evoked potentials could be recorded in the thalamus and in the brain stem after or without bilateral ablation of the cortical visual areas.

Our own findings are in accord with these experimental data and only confirm the well known role of the reticular formation as a nonspecific integrating system of sensory excitations.

On the other hand our interest was aroused by the observation of the daily increase of irradiation of sensory responses to territories as distant as the ventral nucleus of the thalamus and the frontal cortex.

(B) *Morphological Aspects.* The form of the potentials recorded in cortical and subcortical structures assumed two aspects essentially: (1) sometimes the classical form of diphasic rhythmical spikes, representing evoked potentials to each single light flash of a sequence of stimulation were seen. In between each potential the record was low in amplitude, rapid and "desynchronized"; (2) at other times the response assumed the character of a spike and wave complex where each evoked potential was followed by a single slow wave of high amplitude. This second type was chiefly seen in animals which were well accustomed to the experimental conditions and were in a perfectly relaxed state.

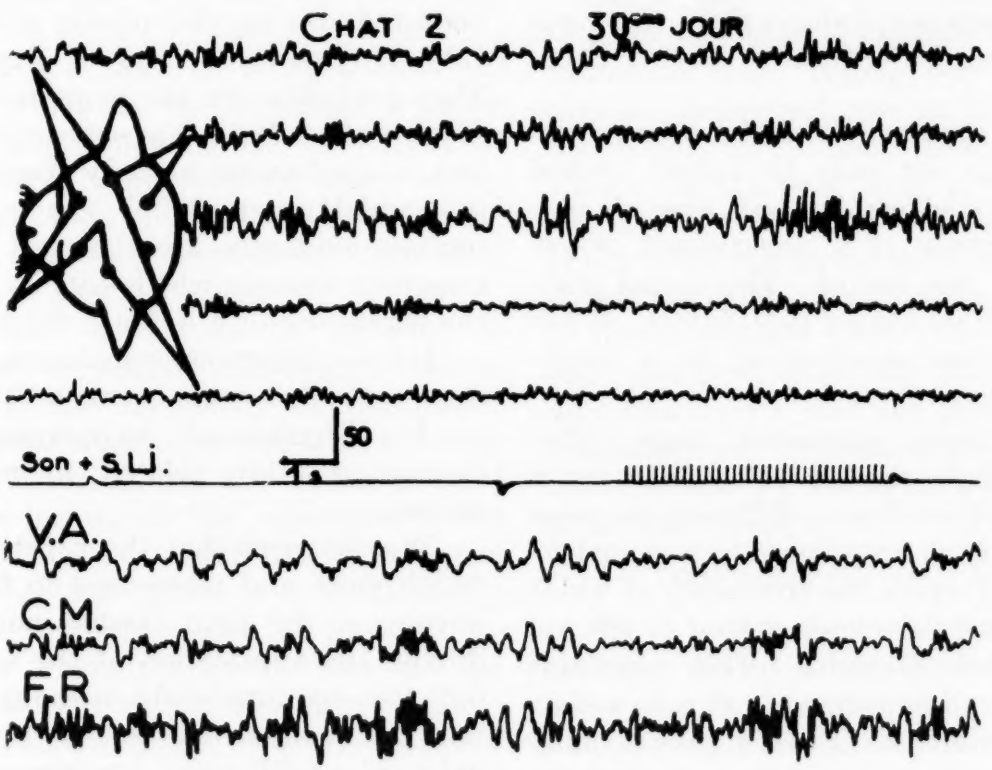

Fig. 11

Cat No. 2. Sudden transition into the state of somnolence. The record is characterized by slow waves and spindles which are not modified by sound stimulation or intermittent photic stimulation.

According to Moruzzi and Magoun (1949) the generalized cortical "desynchronization" corresponds to a state of activation of the reticular formation, whereas the slow synchronization corresponds on the contrary to a state of functional depression of the reticular formation. The finding of gradual transition from generalized desynchronization to regularly recurring waves in the present study may add to the information on the intricate

connections between the diffuse thalamic projection system and ascending reticular activating system discussed since 1949 (Jasper 1949; Hunter and Jasper 1949; Lindsley, Bowden and Magoun 1949).

We may suppose that the two varieties of unconditioned response to intermittent photic stimulation correspond to different states of excitability of the reticular activating system. It will be demonstrated that this hypothesis could be applied to explain the two different morphological aspects of the conditioned electroencephalographic response to the tone stimulus.

II — Electroencephalographic responses to the Conditioned Continuous Sound Stimulus.

During the application of the sound stimulus one is able not only to record evoked potentials (''on effect''), but also a progressive appearance of a generalized desynchronization of the record. The sound stimulus is therefore no longer indifferent. It has assumed a precise significance as a conditioned stimulus.

But at a more advanced stage, after about 4 to 7 days, this desynchronization is progressively replaced by a different response in the form of high amplitude hypersynchronous rhythmical waves, the frequency of which becomes progressively closer to that of the unconditional photic stimulus. This repetitive response appears when the animal is in a state of apparent quietness. Finally, one usually obtains this response during sound stimulation only when the subsequent photic stimulation triggers spike and wave type of discharges. It seems therefore that there is a close relationship between the aspect of the conditioned response and the functional state of the reticular formation. The conditioned response of the ''desynchronized'' type could, therefore, be interpreted as corresponding to a state of reticular activation. Conversely, the hypersynchronous response would correspond to a state of inhibition of the reticular formation. Furthermore, it appeared that this conditioned repetitive response appeared much earlier in mesencephalic and diencephalic structures than in the occipital cortex. This confirms the important role played by the reticular formation in the establishment of conditioned reflexes. One of us (Yoshii 1955) has already pointed out this fact previously.

We were not able to observe the stage of local desynchronization of the activity of the visual cortex as described by Morrell and Jasper (1956). The reason for this is probably that we used bipolar temporo-occipital recordings and that two of our animals became neurotic before this stage could be reached.

The high amplitude and rapid muscular potentials at 25-30 c/sec. observed in the temporo-occipital regions during the duration of the sound stimulus and which frequently persisted during the photic stimulus appear only after several days of experimentation. They probably are the expression of an irradiation of excitation to subcortical motor centres, a mechanism already discussed by Gastaut and Hunter (1950). These muscular potentials evidently are the sign of a state of muscular tension which can be considered as the beginning of a defense reaction.

III — Electroencephalographic Findings during the Intervals between Stimulations.

A. Rhythmical hypersynchronous discharges possibly related to memory mechanisms.

We observed that the repetitive responses which more and more tend to follow the frequency of the light flashes not only appear during the application of the sound stimulus but also spontaneously without any stimulation, as soon as the cat is placed into the habitual conditions of experimentation. These responses predominate clearly in the reticular formation, they are less clear in the centre median and are rarely seen in the occipital regions.

One could object to this by saying that these hypersynchronous discharges are merely the consequence of the presence of permanent electrodes within the reticular formation. Around these electrodes there is also always a small necrotic lesion, which even if minimal could evoke slow wave discharges. However, we do not consider this objection as well founded and we think of being able to refute it on the basis of the following arguments:

(1) The repetitive bursts are not of a random frequency, but follow that of the unconditioned stimulus. Thus they are at 4

c/sec. if one uses a flickering rhythm at this 4 c/sec. frequency, they are at 5 or 10 c/sec. when the intermittent photic stimulation is at 5 or 10 c/sec. and in this latter case one cannot even call them slow waves any more.

(2) The repetitive bursts disappear as soon as the animal is placed in a neutral room, or transferred into a different environment. They also disappear during the stage of experimental neurosis.

(3) The bursts are morphologically identical to those which appear during sound stimulation in the occipital cortex where no electrode is implanted into the cerebral substance.

(4) Finally it may be recalled that the rhythms recorded in the intervals between stimulations and following the frequency of the light flashes were already observed by Livanov (1945, 1948) and Ulett (1955) in the visual cortex of animals repeatedly stimulated by intermittent photic flashes.

We therefore believe to be justified to consider these repetitive discharges which follow the specific frequency of the photic stimulation as a conditioned response, not only to the sound stimulus, but also to the general conditions under which the experiments are conducted. We even would like to advance the hypothesis that there is a relationship between these discharges and the physical expression of a mnemonic trace. Was not the reticular formation within the larger framework of the centrencephalic system considered by Penfield (1954) as the structure where memory mechanisms were integrated ? The rhythmical aspect of the electrical expression of the mnemonic trace was predicted by Grey Walter in 1950 who demonstrated the advantage of an ''oscillatory'' theory of memory and who concluded ''until there is very strong evidence to the contrary I suggested that rhythmic oscillation between cerebral elements as a physical basis for short-term memory is a fertile working hypothesis''.

B. Progressive synchronization of the electrical activities of the reticular formation and the occipital cortex.

It is well known that there are no precise relationships between the electrical activity of the cortex and that of subcortical structures, even when they are recorded in structures closely connected with each other as the specific thalamic nuclei and their cortical projection areas.

We therefore attribute a great importance to the fact that the absence of synchrony between the activity of the reticular formation and of the visual cortex observed before conditioning is gradually replaced during conditioning by a clear synchronization of spontaneous bursts occurring in these two cerebral structures.

Without going into a renewed discussion of the theory of reverberating circuits which would in any case be insufficient to explain this phenomenon, it appears to us essential to emphasize this ''tuning process'' which may play an important role in the elaboration of the memory mechanisms previously mentioned. These observations also give some supplementary demonstration of the establishment of connections between subcortical and cortical structures during conditioning. It remains to be shown whether this ''reticulo-occipital tuning'' observed when the unconditional stimulus was light could not become a ''reticulo-temporal'' or ''reticulo-central tuning'' when the stimulus is a sound or a somesthetic stimulus, respectively.

CONCLUSIONS AND SUMMARY

In 4 cats the electroencephalographic changes recorded in the cortex, the thalamus and the mesencephalic reticular formation during conditioning were studied. Conditioning was produced by coupling of an unconditioned light stimulus in the form of intermittent photic stimulation with a preceding conditional auditory stimulus in the form of a continuous sound. This study allows to draw the following conclusions:

1. The results confirm certain findings obtained in investigations carried out in the recent years. The appearance of evoked potentials and of a desynchronization during the presentation of the conditioned stimulus characterizes the first stage of conditioning. During a second stage the desynchronization is replaced by hypersynchronous repetitive discharges which progressively tend to follow the frequency of the intermittent photic stimulation. The so-called stage of experimental neurosis is characterized by the alternation

of rapid patterns with sleep patterns during which the conditioned electroencephalographic responses characterized by desynchronization or by specific rhythmic discharges disappear.

2. The role played by the reticular formation in the elaboration of conditioning processes is again stressed:

(*a*) the conditioned specific responses are of earlier onset, higher amplitude and are more stable in the reticular formation;

(*b*) the daily repetition of the experiments progressively increases the relationships of phase, form and amplitude between the bursts and other electrographic elements recorded in the occipital cortex and in the reticular formation without any stimulation.

3. A new finding was obtained in this study: the spontaneous appearance without any stimulation of repetitive discharges at the frequency of the photic flashes and almost exclusively recorded from the reticular formation. These rhythmic discharges appear as soon as the animal is placed in the habitual conditions of the experiment. They could represent an elementary electrographic manifestation of a memory process.

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CORTICAL AND SUBCORTICAL ELECTROGRAMS IN ANESTHESIA AND ANOXIA IN MAN [1]

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Recent advance in the study of depth electrography on the human subjects (Hayne *et al.* 1949; Spiegel *et al.* 1951, 1956; Delgado *et al.* 1953, 1956; Sem-Jacobsen *et al.* 1953, 1955, 1956; Okuma *et al.* 1954; Heath 1954; Schwartz *et al.* 1956; etc.) has provided much knowledge on the brain in various functional states. This report covers the effect on the cortical and depth electrograms by administration of intravenous and intramuscular barbiturates, rectal chloral hydrate, subcutaneous and intravenous Benadryl, inhalation of trichloroethylene and pure nitrogen gas. The effects of intravenous barbiturate and subcutaneous scopolamine hydrobromide on the electrogram were reported earlier (Okuma *et al.* 1954). In the light of these findings the neural mechanisms underlying altered consciousness will be discussed and action of drugs on the central nervous system will be reconsidered.

TECHNIQUE

Recording of cortical and depth electrograms was performed on 74 patients (parkinsonism 43; double athetosis 9; epilepsy 7; feeblemindedness 4; other organic brain diseases 11) in whom stereoencephalotomy on the basal ganglia was indicated and whose electrograms could be registered in the resting state. Patients with normal or almost normal routine EEGs were selected.

Our technique using multi-lead needle electrode was described previously (Okuma *et al.* 1954). A multi-lead needle electrode 1 mm. in diameter with 8 recording tips at intervals of 1 cm. was inserted stereotaxically from the central region into the medial thalamus and other subcortical structures according to their coordinates and was fixed to the skull as illustrated in figure 1. In most cases monopolar recordings with reference ear electrodes and bipolar recordings with electrodes linked in sequence were used and occasionally conventional scalp EEGs simultaneous with the cortical and depth recordings were obtained. All electrograms were recorded with an 8-channel Sanei Model I electroencephalograph (time constant 0.3).

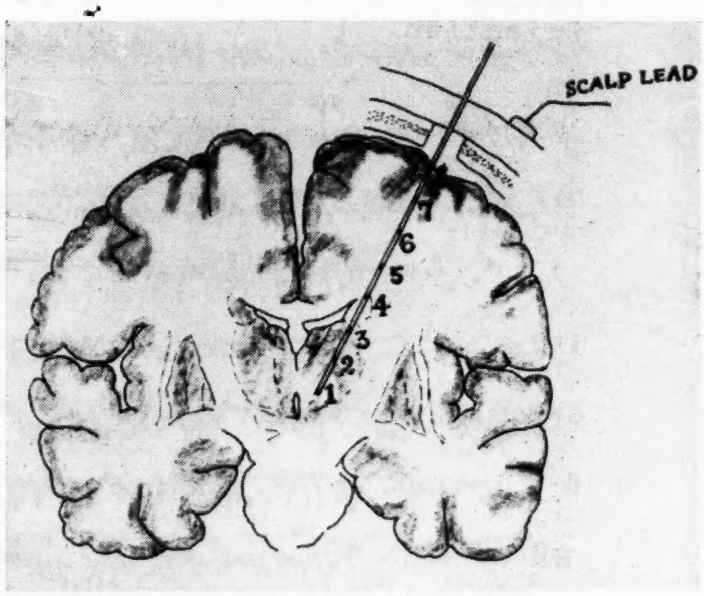


Fig. 1

Schematical diagram of a multi-lead needle electrode. Electrode 1 lies in the medial nucleus of the thalamus and electrode 8 on the surface of the central cortex. Distance of electrodes is 1 cm.

Surgical placement of the depth electrode was carried out under local anesthesia. Electrograms of the cortex and deeper structures as well as scalp were registered for about 20 min. in the non-anesthetized state as a control. Techniques of inducing anesthesia and anoxia are described in detail under each paragraph.

[1] Presented at the 3rd Annual Meeting of the Japan EEG Society (April, 1954) and at the 5th Meeting of the German EEG Society (September, 1955).

RESULTS

I. *Intravenous and intramuscular injection of thiopental sodium.*

As reported previously, when 2.5 per cent solution of thiopental sodium was injected intravenously at the rate of 2 cc. per min., fast activity in the cortical electrogram with rising amplitude appeared early followed by a gradual decrease in frequency. In a few minutes alpha activity disappeared and was replaced by 2 to 6/sec. waves in cortical and depth electrograms as the subject loses consciousness.

Figure 2 shows electrograms of a patient in whom thiopental sodium was injected intravenously and who was ordered to pull on a string following examiner's calling of numbers (when the string is pulled a signal is recorded on the EEG tracing). As narcosis deepened fast activity with increasing voltage appeared in surface and also in depth electrode tracings. Alpha activity, however, persisted in the cortical and depth electrograms as long as the subject could pull on the string, though it showed gradual slowing. In the stage of transition to unconsciousness, as shown to the right of figure 2, high voltage slow waves of 2 to 6/sec. appeared in both cortical and depth electrograms, but they were suppressed and replaced by fast activity during the period in which the subject was pulling the string and appeared only in the intervals of those pulling actions. The subject could no longer respond to the call "67" and no response was seen on the tracings, which showed continuous slow waves of 2 to 6/sec. thereafter.

Effect of intramuscular injection of the same drug on the cortical and depth electrograms (fig. 3) is somewhat different from that caused by intravenous administration and is noted in table I.

The spindle burst appeared simultaneously and almost synchronously in the cortical and thalamic electrograms but the amplitude of cortical spindle bursts was larger than that of the thalamic electrogram in both monopolar and bipolar recordings. These spindle waves reversed their phase in both cortical and thalamic levels when recorded bipolarly.

Electrographic changes at the time of intramuscular injection of thiopental sodium are summarized as follows: the enhancement of cortical fast activity is less than that by intra-

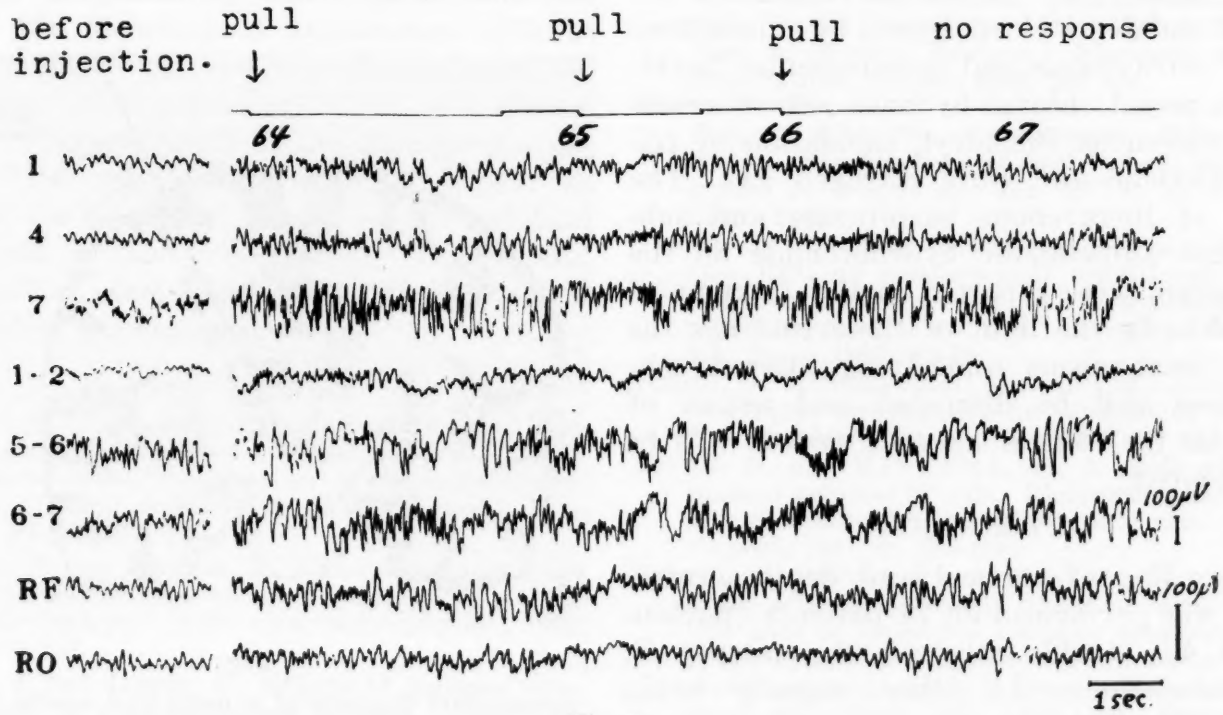
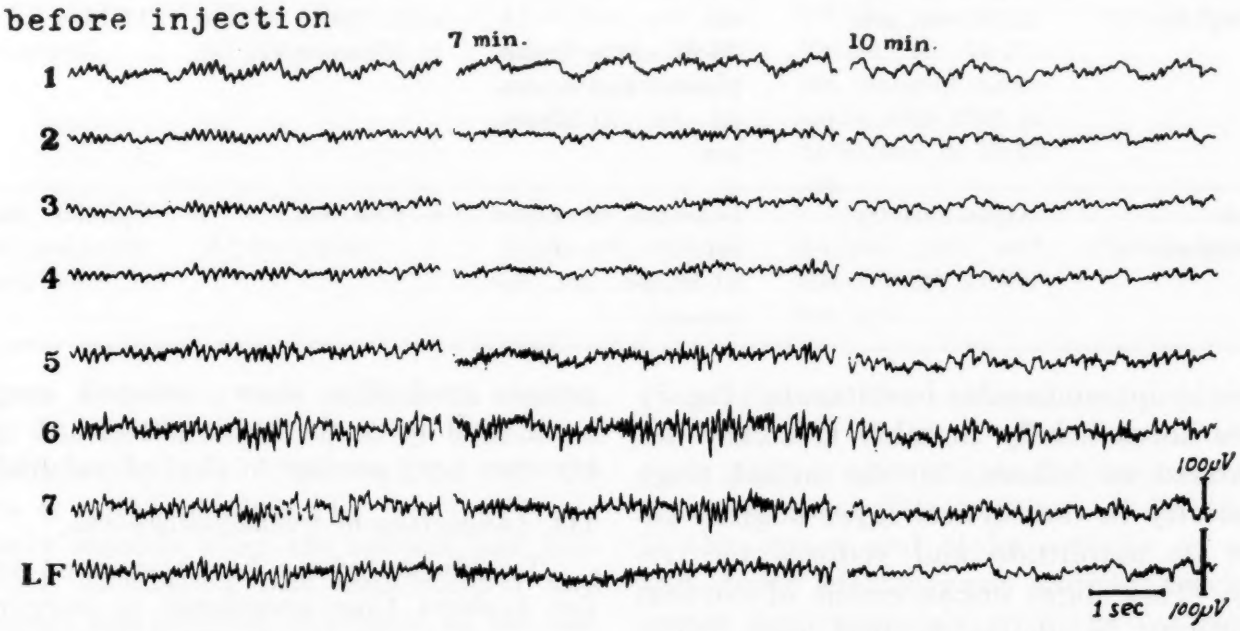


Fig. 2

Effect of intravenous thiopental sodium. Left: before injection. Right: stage of transition to the loss of consciousness (the amount injected is 0.2 g.). The line at the top of the tracing is lowered when the subject pulls the string in response to the examiner's calling of numbers. Note that when the subject pulls the string, slow waves are replaced by fast activity. The subject could not respond to the call 67 and slow waves predominate afterwards.

venous injection, though slight increase in amplitude is observed initially, and the wave pattern changes resemble those of natural sleep except for the large cortical fast activity.

The electrogram of the caudate nucleus during barbiturate anesthesia is shown in figure 4. A multi-needle carrying 4 electrodes was inserted in the head of the caudate nucleus. Electrodes 10 and 11 (electrodes distance 1 cm.) were in the caudate, 13 was on the surface of the premotor cortex and 12 1 cm. below the surface. As shown on the left in figure 4, electrograms from the caudate and thalamus were similar, containing chiefly alpha activity mixed with a small amount of low voltage fast activity. Intravenous injection of 2.5 per cent thiopental sodium at the rate of 2 cc. per min. produced gradual suppression of caudate nucleus alpha activity and appearance of 4-7/sec. waves. When the subject reached the deepest stage of anesthesia, 0.5 to 3/sec. slow waves of 100 to 200 μV. or over predominated. The stage of activation of



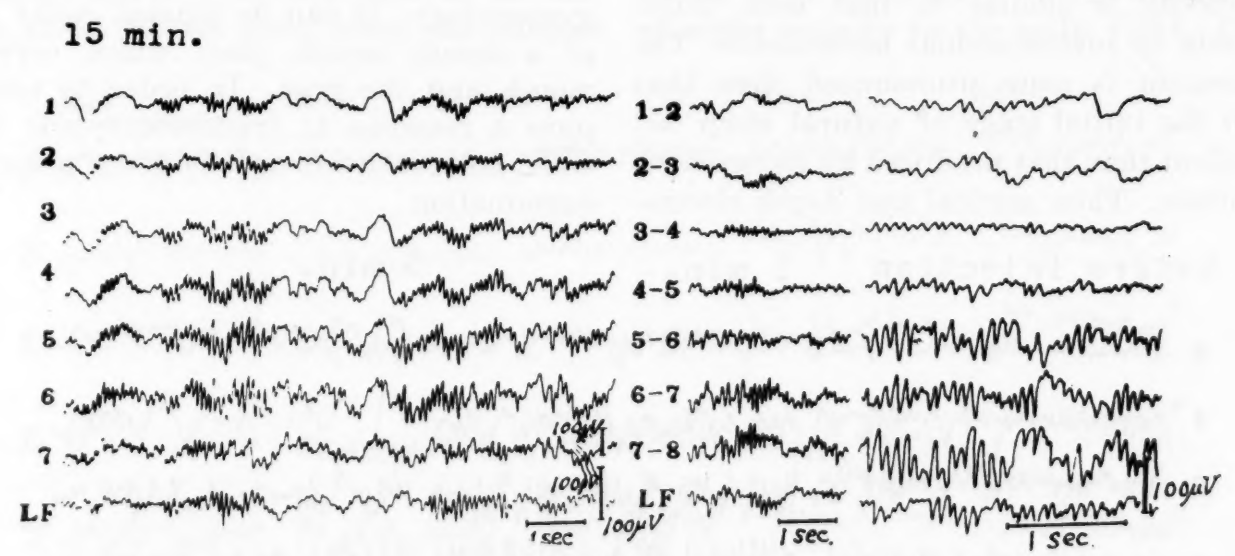


Fig. 3

Effect of intramuscular thiopental sodium (0.5 g.). When the subject becomes drowsy (7 min.), fast activity in the cortical region increases, while alpha activity in the cortex and depth is depressed. Ten minutes after the beginning of injection fast activity shows reduced voltage again and slow waves of around 6/sec. appear in both regions.
Lower tracings show spindle phase. Phase reversal both in the level of cortex and depth.

the caudate on which Schneider *et al.* (1952) had reported on cat was not observed in man.

II. *Rectal administration of chloral hydrate.*

Electrographic changes produced by rectal administration of chloral hydrate (aqueous solution of 3 g. of chloral hydrate) are similar

TABLE I

ELECTROGRAPHIC CHANGES BY INTRAMUSCULAR THIOPENTAL SODIUM

Time after injection	Before	7-10 min.	10-15 min.	15 min.
State of the subject	Awake	Drowsy	Very light sleep	Light sleep
Cortical electrogram	Alpha activity 13-30/sec. act.	Decrease of alpha act. 13-20/sec. act. suppressed and replaced by 21-30/sec. act.	4-7/sec. act. mixed with low voltage 21-30/sec. act.	Spindle burst of 12-14/sec.
Thalamic electrogram	Alpha activity	Decrease of alpha act. 21-30/sec. act. increased.	4-7/sec. act.	Spindle burst of 12-14/sec.

to those by intramuscular barbiturate (fig. 5) and are noted briefly in table II. They are summarized as follows. In the initial stage fast activity in the cortical layer slightly increases its amplitude and reduces its frequency. This slight enhancement of cortical fast activity is similar to that seen under anesthesia by intramuscular barbiturate. The enhancement is more pronounced than that seen in the initial stage of natural sleep but less evident than that produced by intravenous barbiturate. Then cortical and depth electrograms gradually show reduced amplitude again and later the wave pattern in general becomes very similar to that of natural sleep.

III. *Inhalation of trichloroethylene.*

Trichloroethylene has been used recently for a short time anesthesia in surgery and gynaecology. It can be inhaled easily by use of a simple mouth piece which covers the mouth and the nose. In order to secure as pure a response to trichloroethylene as possible, no sedative drug was given prior to the examination.

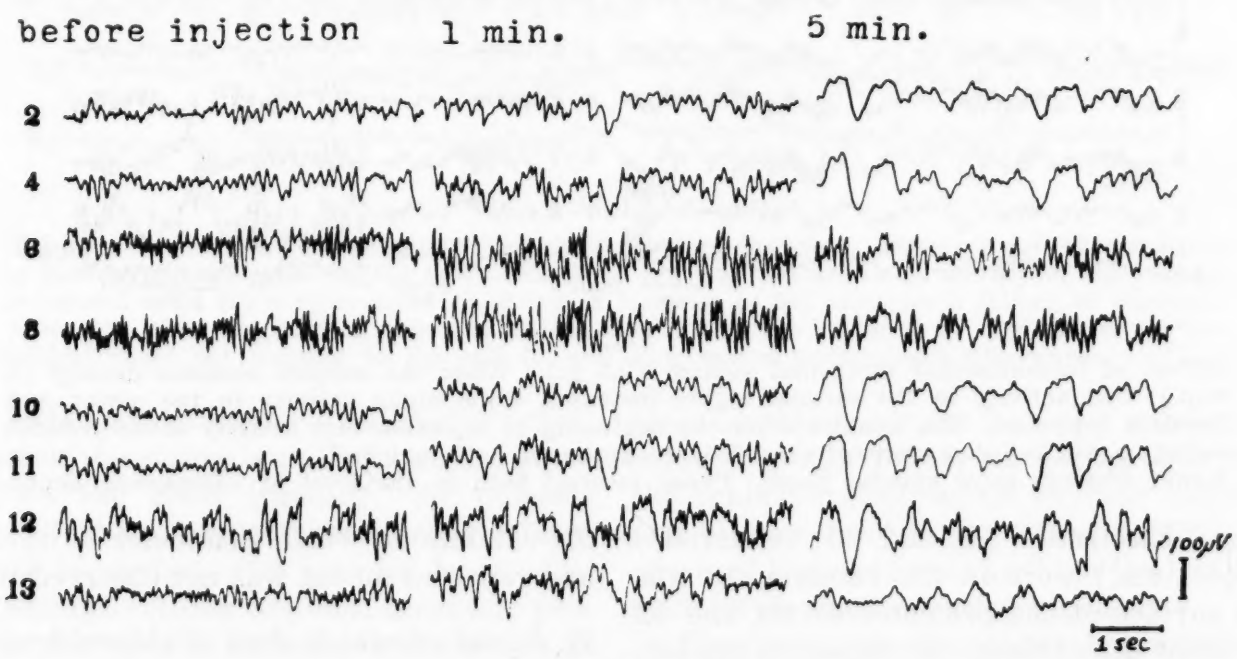


Fig. 4

Progressive changes of the electrogram of the caudate nucleus under intravenous thiopental sodium. 2: thalamus. 6, 8: central cortex. 10, 11: caudate. 12, 13: premotor cortex. Electrograms of the caudate show similar changes to those of the thalamus. See text.

TABLE II

ELECTROGRAPHIC CHANGES BY RECTAL CHLORAL HYDRATE

Time after administration	Before	10 min.	15 min.	30 min.
State of the subject	Awake	Drowsy	Very light sleep	Light sleep
Cortical electrogram	Alpha activity 13-30/sec. act.	13-20/sec. act. reduced and 21-30/sec. act. predominated	4-7/sec. act. Period of 13-20/sec. activity alternated with that of 21-30/sec. in 10-60 sec.	Spindle burst
Thalamic electrogram	Alpha activity	Alpha act. reduced	4-7/sec. act. and low voltage 21-30/sec. act.	Spindle burst

Figure 6 shows a case studied on electrographic changes brought about by inhalation of trichloroethylene. The outline of the changes is noted in table III.

Thirty seconds after the subject lost consciousness, inhalation was discontinued and the subject was allowed to respire in the air. It was about 10 sec. later when the subject responded to the command to open his eyes. Cortical and thalamic electrograms changed their pattern abruptly as the subject regained consciousness. The voltage of fast activity in the cortex and alpha activity in cortical and depth electrograms showed marked increase simultaneously with the reappearance of alpha activity in the scalp EEG. Cortical

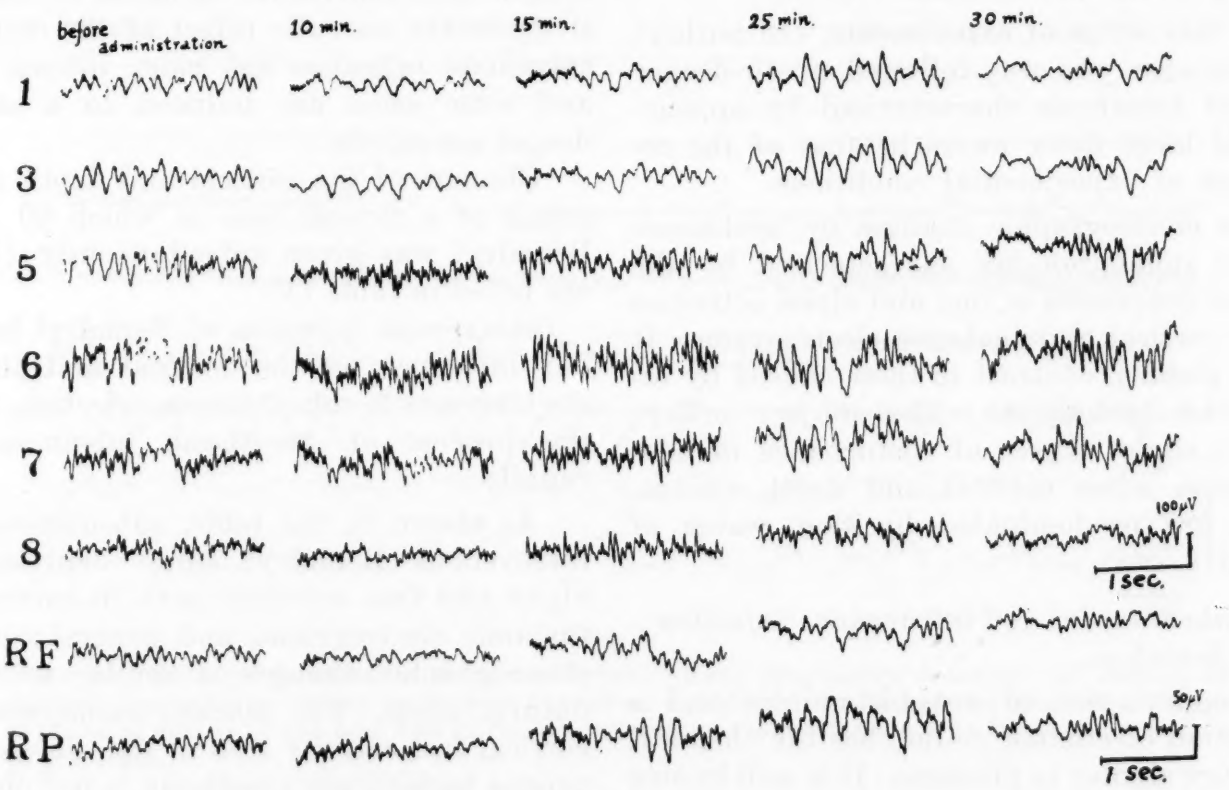


Fig. 5

Changes induced by rectal chloral hydrate (3 g.). When the subject becomes drowsy (10 min.), low voltage fast activity increases with disappearance of alpha activity. During very light sleep (15 min.) stage of higher voltage fast activity alternates with that of lower voltage. Then slow waves of 4-7/sec. appear in cortex and depth (25 min.). This stage is followed by spindle phase (30 min.).

TABLE III

ELECTROGRAPHIC CHANGES BY TRICHLOROETHYLENE INHALATION
(BIPOLAR RECORDING)

Time after inhalation	Before	30 sec.	90-150 sec.	250 sec.
State of the subject	Awake		Slight turbidity of consciousness but responsible	Unresponsive to call by name
Cortical electrogram	Alpha activity 13-30/sec. act.	Voltage reduction of alpha and 13-20/sec. act. 21-30/sec. act. predominated	Almost same as 30 sec. Random 4-7/sec. activity	4-7/sec. activity predominated Remarkable voltage reduction of 10-30/sec. activity
Thalamic electrogram	Low voltage alpha act.	Decrease of alpha act. Low voltage 21-30/sec. act.	Random 4-7/sec. activity	Almost flat with low 4-7/sec. activity

electrogram, however, showed more fast activity of 13 to 20/sec. with lower voltage and less alpha activity than that of pre-inhalation period. The voltage of thalamic alpha activity was also lower in that stage. It was about 5 min. later when wave pattern recovered to the pre-inhalation level.

In this series of experiments, the authors have no case who was followed up to deeper stage of anesthesia characterized by appearance of large delta waves because of the restriction of experimental conditions.

The electrographic changes by trichloroethylene inhalation are characterized by the parallel depression of fast and alpha activities in the cortical and thalamic electrograms. It makes a sharp contrast to those caused by intravenous barbiturate. The subject suffers from a slight degree of disturbance of consciousness when cortical and depth electrograms are predominated by slow waves of around 6/sec.

IV. *Subcutaneous and intravenous injection of Benadryl.*

Benadryl, one of anti-histaminics and a derivation of ethanol amine, has the chemical structure similar to procaine. It is well-known that Benadryl has sedative or narcotic effect on the central nervous system and drowsiness or sleepiness is a chief side-effect of the drug. Some authors think that Benadryl affects the cerebral cortex and others suggest it blocks the function of the subcortical structure (Tanaka 1951).

When Benadryl is injected subcutaneously, most of the subjects show more or less alteration of consciousness ranging from slight drowsiness to sleep-like state, though there is considerable individual variation in the sensitivity to the narcotic effect of the drug. Intravenous injection has more intense effect and some cases are induced to a state of deeper anesthesia.

Changes of the cortical and depth electrograms of a typical case in which 60 mg. of Benadryl was given subcutaneously (fig. 7) are noted in table IV.

Intravenous injection of Benadryl has similar influence on the cortical and thalamic electrograms to subcutaneous injection, though the process of anesthesia advances more rapidly.

As shown in the table, subcutaneous and intravenous Benadryl cause depression of alpha and fast activities both in cortical and thalamic electrograms, and general course of electrographic changes is similar to that of natural sleep. The marked enhancement of cortical fast activity seen at the time of intravenous barbiturate anesthesia is not observed.

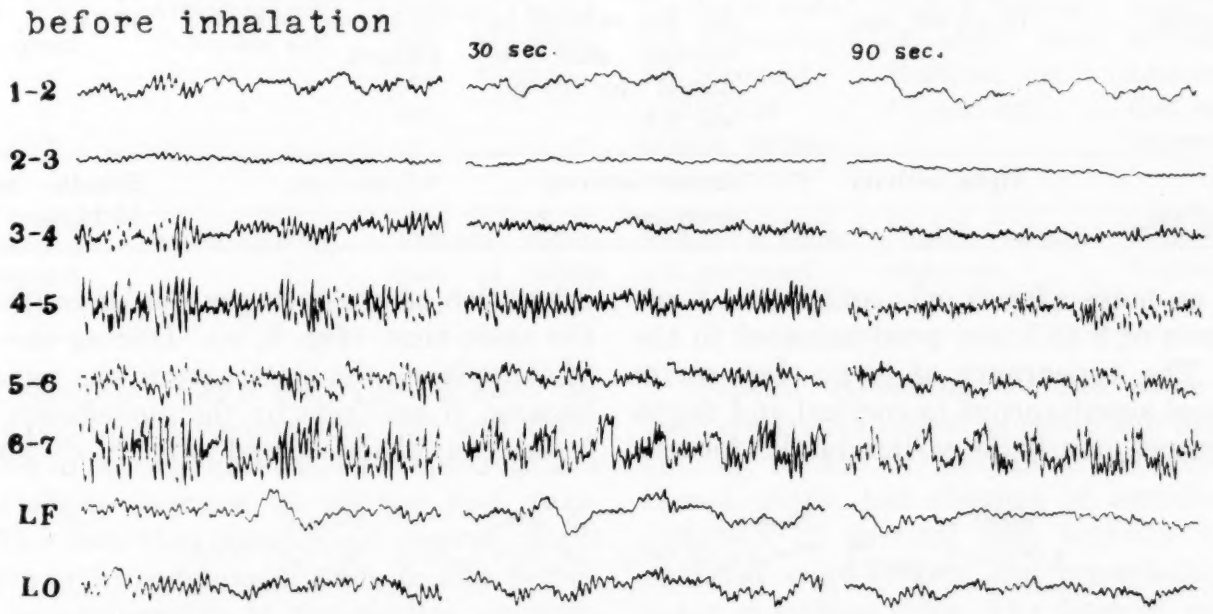
V. *Inhalation of pure nitrogen gas.*

There have been many studies of the effect of anoxia or hypoxia on the electrical activity of the brain and the state of consciousness,

but relationships between the electrographic changes of the cerebral cortex and deeper structures and alteration of consciousness have not yet been investigated on the human subject.

In our cases, nitrogen gas was inhaled by use of a rubber mouth piece with two outlet covered with valves, which prevent nitrogen gas from mixing with expired air. The mouth piece was connected to a large Douglas bag filled with nitrogen gas. The subject was ordered to count on his fingers following the examiner's repeated callings of numbers from 1 to 10 and the time when he discontinued to count was taken as a sign of loss of consciousness. After a few minutes of respiration in the air with scalp and depth electrodes and a mouth piece attached on the subject, nitrogen gas was sent to the mouth piece.

Figure 8 shows a typical course of electrographic changes at the time of nitrogen inhalation recorded by monopolar method. The outline of the electrographic changes is noted in table V.



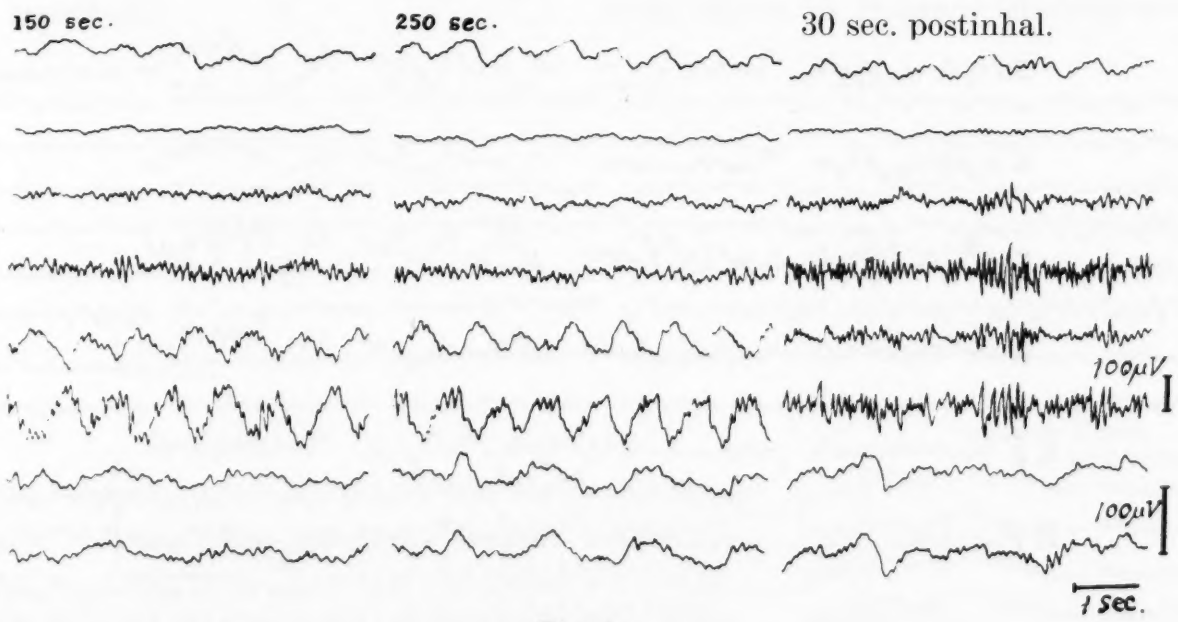


Fig. 6

Recording during inhalation of trichloroethylene. Note progressive reduction of voltage of cortical fast activity. Alpha activity in the cortex and depth also disappears gradually. Large rhythmical swings of the base line in the lower tracings are artifacts due to increased pulsation of the brain.

About 55 sec. after the beginning of inhalation when the subject could count on

TABLE IV

ELECTROGRAPHIC CHANGES BY SUBCUTANEOUS BENADRYL

Time after injection	Before	10 min.	15 min.	20 min.
State of the subject	Awake	Drowsy	Very light sleep	Light sleep
Cortical electrogram	Alpha activity. 13-30/sec. act.	Alpha and 13-20/sec. act. reduced in voltage and replaced by 21-30/sec. act.	4-7/sec. act. 21-30/sec. act. decreased	Spindle burst of 12-14/sec.
Thalamic electrogram	Alpha activity	Alpha activity decreased	4-7/sec. act.	Spindle burst of 12-14/sec.

fingers no more (fig. 8, a), continuous large slow waves of 2 to 5/sec. predominated in the record. The appearance of large slow waves was almost simultaneous in cortical and depth electrograms or a little earlier in the former. inhalation of nitrogen gas was discontinued at the same time (fig. 8, b). During the period of convulsion, the electrogram was unreadable because of artifacts by the movements. After 5 sec. convulsion ceased (fig. 8, c) and slow

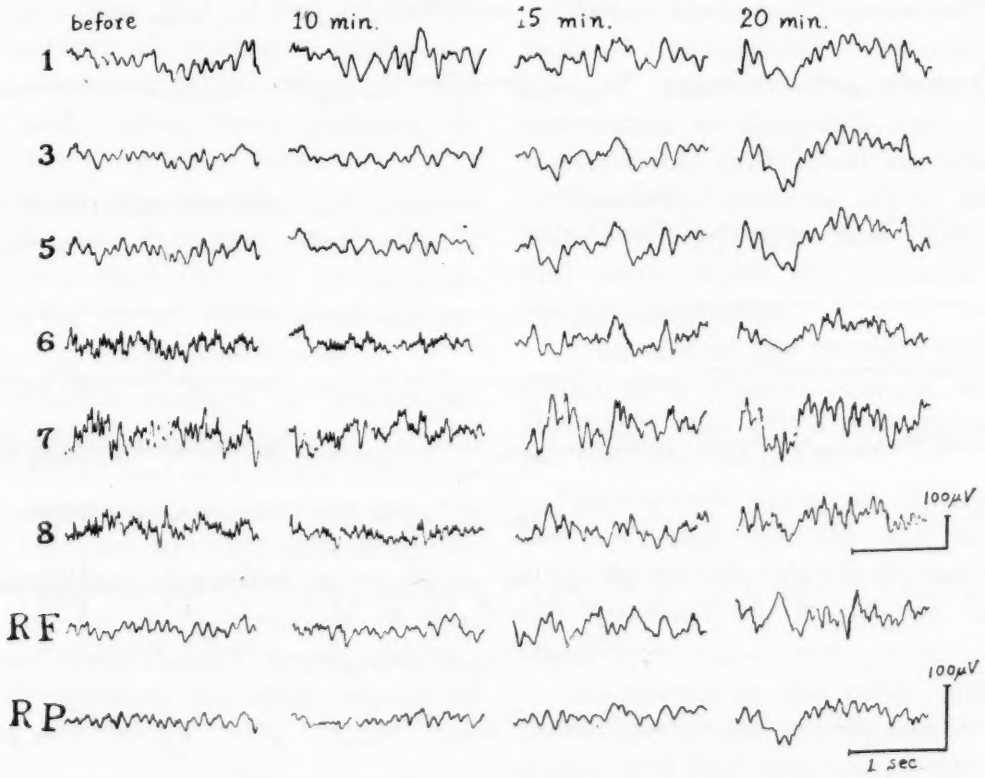


Fig. 7

Effect of subcutaneous Benadryl (60 mg.). Fast and alpha activities in the cortex and depth show reduced voltage as the subject becomes drowsy (10 min.). Then 4-7/sec. activity (15 min., very light sleep) and spindle bursts (20 min., sleep) appear in all leads.

Loss of consciousness appeared to coincide with the continuous appearance of those slow waves in the cortical and depth electrograms. Five seconds after the subject lost consciousness, slight myoclonic convulsion occurred and waves of 6/sec. appeared as a burst in cortical and depth electrograms for 2 to 3 sec. The subject began to count on fingers again at d (fig. 8) and the electrographic pattern became similar to that of the pre-inhalation

TABLE V

ELECTROGRAPHIC CHANGES BY NITROGEN GAS INHALATION

Time after inhalation	Before	10-20 sec.	30-40 sec.	45-50 sec.	55 sec. —
State of the subject	Awake	:	:	:	Unconscious
Cortical electrogram	Alpha activity. 13-30/sec. act.	Voltage reduction of alpha and 13-20/sec. act.	Voltage of alpha and 13-20/sec. act. increased Activity of around 15/sec. predominated	Higher voltage of alpha and 13-20/sec. act. 4-7/sec. act.	High voltage 2-5/sec. act. Low voltage fast act. superimposed
Thalamic electrogram	Alpha activity	Voltage reduction of alpha act.	Voltage of alpha act. increased	Higher voltage alpha act.	High voltage 2-5/sec. act.

period abruptly. For a few minutes after the subject regained consciousness, fast and alpha activities in cortical and thalamic electrograms showed slight increase of voltage and duration. The fact that the subject showed slight euphoria or hypomaniacal state in this period might be comparable to the similar phenomenon observed during recovery from barbiturate anesthesia.

Bipolar recording on the same subject with electrodes linked in series showed similar finding to that of monopolar recording mentioned above, but changes of amplitude and duration of cortical fast activity could be revealed more clearly and remarkably by bipolar recording (fig. 9). Loss of consciousness was coincident with the appearance of delta waves in thalamic electrogram. These

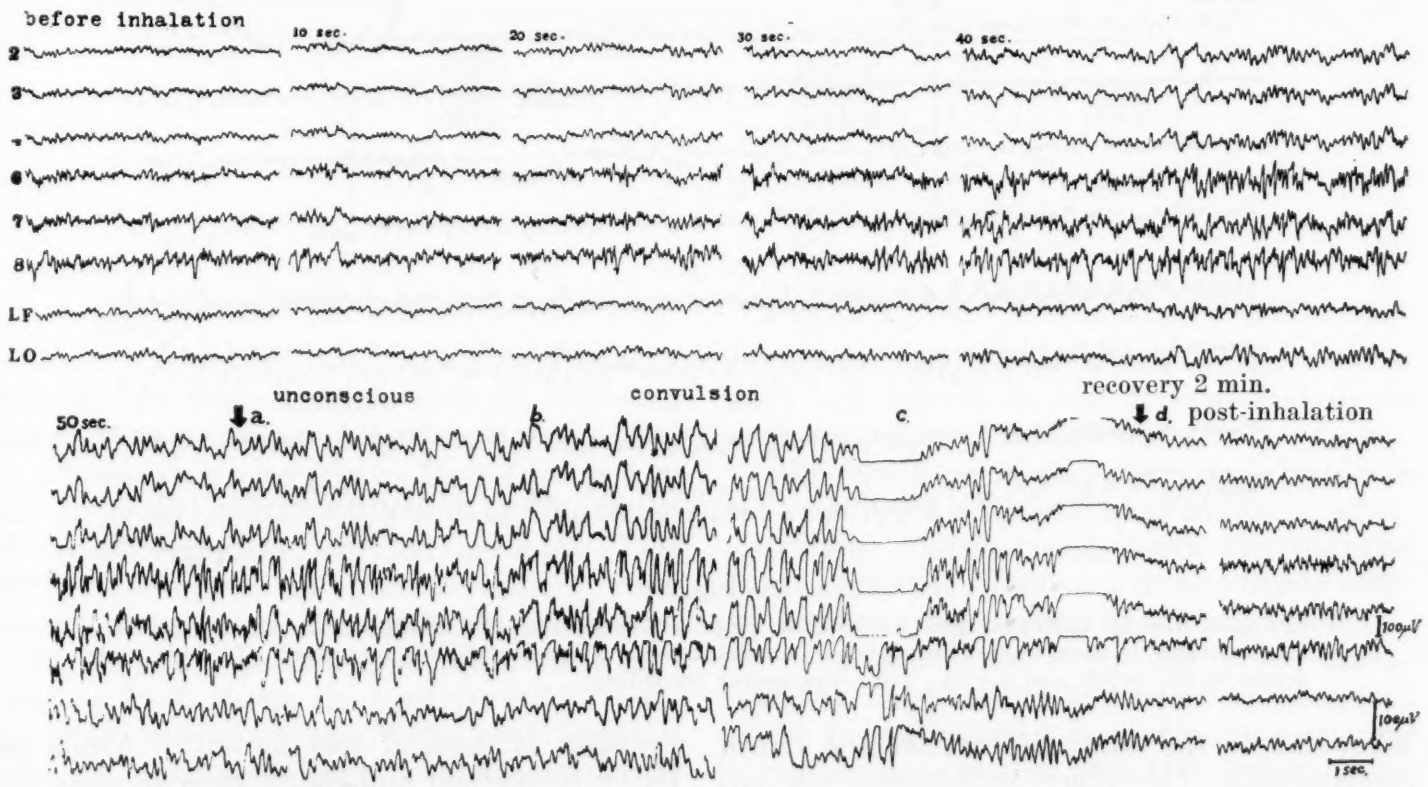


Fig. 8

Changes during nitrogen gas inhalation (monopolar recording). Fast activity in the cortical electrogram shows increased amplitude and duration and slow waves of around 6/sec. appear in the cortex and depth (30-40 sec.). Then slow waves of 2-5/sec. predominate (50 sec.) and the subject loses consciousness (a); b-c: clonic convulsion; d: the subject regained consciousness.

changes of fast activity in the cortex which is easily revealed by use of direct recording can hardly be detected by investigation of electroencephalogram led via scalp.

COMMENT

Electrographic changes induced by various anesthetic drugs are divided into three groups according to the study of cortical and depth electrograms. (1) When barbiturate was administered intravenously, fast activity in the cortical layer showed remarkable increase of amplitude and duration in the initial stage (fig. 10, G). Then alpha activity in cortical and depth electrograms disappeared and was replaced by large theta and delta waves when the subject lost consciousness (fig. 10, H and I). (2) Inhalation of trichloroethylene, subcutaneous and intravenous injection of Benadryl, subcutaneous injection of scopolamine hydrobromide (reported in previous paper, Okuma *et al.* 1954) produced gradual depression of cortical fast activity. Alpha activity in cortical and depth electrograms disappeared gradually and was replaced by theta waves (fig. 10, B and C). These changes were similar to those of natural sleep. (3) Rectal administration of chloral hydrate and intra-

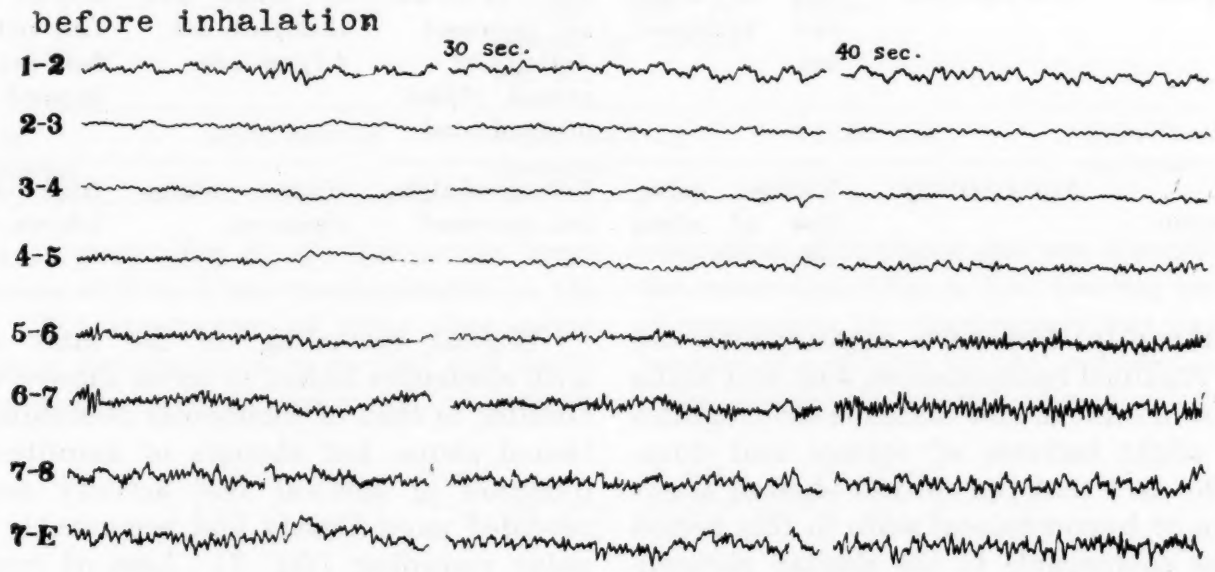


Fig. 9

Changes during nitrogen gas inhalation (bipolar recording). Enhancement of the cortical fast activity is seen evidently. Loss of consciousness coincides with appearance of large slow waves in the depth and cortex. 7-E: monopolar recording.

muscular injection of barbiturate temporarily caused slightly increased amplitude of cortical fast activity initially, with reduced incidence and voltage of alpha activity (fig. 10, E). After a while theta waves predominated in the record (fig. 10, F) and then a shift to the spindle phase followed. The third group of wave pattern is intermediate between the first and the second group. In most cases a spindle phase occured (fig. 10, D).

The difference of wave pattern in various anesthesias was probably due to several factors. The first was the difference in the anesthetic drug itself. There are considerable variances between the electrographic changes following intravenous injection of barbiturate, classified as a brain stem narcotic by Pick (group 1 in our division), and those caused by inhalation of trichloroethylene, cortical narcotic (Pick 1927) (group 2 in our division). Subcutaneous injection of scopolamine hydrobromide, though classified as a brain stem narcotic by Pick, shows the electrographic changes of the second group. When barbiturate is injected intramuscularly, enhancement of cortical fast activity is not so remarkable as that produced by the same drug administered intravenously, and the changes are classified as the third group in our division.

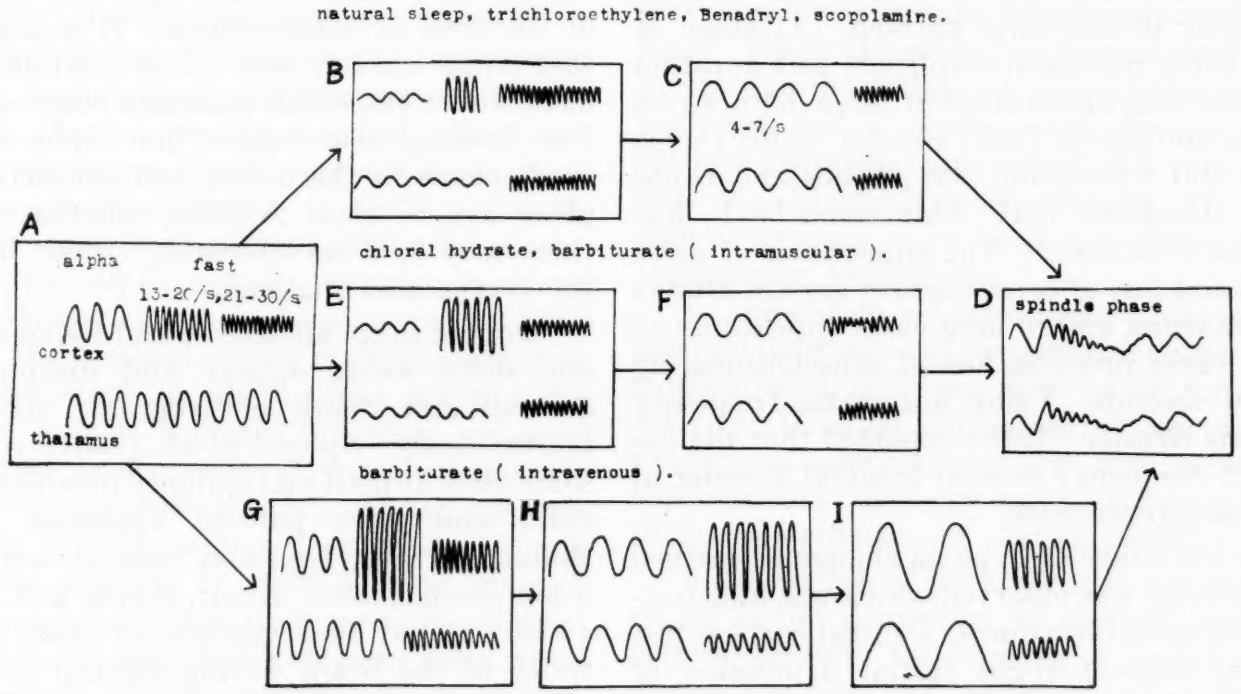


Fig. 10

Schematical illustration of changes of the cortical and depth electrograms in various anesthesias. See text.

These facts suggest that electrographic changes in anesthesia can be explained not only by the difference in the drug, but in the mode of administration. The method of administration results in variations of drug concentration in the blood and brain and influences the rate of increase and decrease of the effective concentration. Nervous system function is probably disturbed more severely with higher concentrations of drug. It is, of course, impossible to compare the action of all anesthetic drugs with similar methods of administration, but in the present study each anesthetic, if possible, was given in different ways and effects on the cortical and depth electrograms were compared.

The electrogram following Benadryl does not vary much with different routes of administration. Cortical and depth electrograms showed gradual diminution of amplitude without marked enhancement of cortical fast activity even when the drug was given intravenously. Apparently the action of Benadryl on the central nervous system is not so strong in a given dose as that of barbiturate and the influence of the drug on nervous tissue does not depend on the method of giving it.

These facts indicate that change of the electrical activity of the brain at the time of

anesthesia is a function of several variables: chemical structure of the drug, effective concentration of the drug in blood, the rate of increase and decrease of the concentration, affinity of the drug to any specific structure of the brain, etc.

Since the initial report by Berger, there have been many studies on the electroencephalogram during anoxic state in man. In general electroencephalographic changes during anoxia or hypoxia may be divided into four stages: (1) stage of little alteration in EEG, (2) stage of decreased amplitude and duration of EEG, (3) stage of increased amplitude and duration of EEG and also of regularity of the wave pattern, (4) stage of remarkably increased amplitude and duration of waves with appearance of large delta waves (Gibbs and Davis 1935; Bremer 1936; Davis, Davis and Thompson 1938; Gibbs and Gibbs 1941; Motokawa 1947; Shimazono 1951; Kasamatsu 1952; etc.). The appearance of delta waves and loss of consciousness are not always simultaneous, and in most cases appearance of delta waves precedes loss of consciousness by several seconds. Using automatic frequency analysis Brazier (1948) reported that the dominant frequency showed gradual slowing at reduced oxygen level.

In our study of hypoxia change of cortical fast activity was observed which was undetectable via scalp recordings. Central cortical fast activity showed slight initial depression of amplitude followed by gradual increase of amplitude and duration. In one case delta waves were not evident and only the slowing and enhancement of cortical fast activity were observed during loss of consciousness. Our findings suggest a correlation between cortical fast activity and cerebral cortical dysfunction with altered consciousness.

Delta waves appear from cortex and deep structures almost simultaneously or a little earlier in the cortical electrogram as hypoxia progresses and loss of consciousness coincides with the continuous delta waves in the cortex and thalamus.

There have been many studies on the changes in electrical activity of the brain of experimental animals under hypoxia or ischemia. Differences in the tolerance of various parts of the central nervous system to ischemia were reported by Sugar and Gerard in 1938, but most of the reports indicate that the electrical activity of the cerebral cortex and subcortical nuclei disappears simultaneously in advancing ischemia (Gänshirt *et al.* 1952; Jung 1953; Hirai *et al.* 1956). The diverse findings in animal and human subjects may be due to differences in experimental conditions and varying tolerances of human and animal brains to the hypoxic state.

Alpha activity is recordable from wide areas of the brain and shows parallel changes in the cerebral cortex and subcortical regions during sleep, anesthesia and other alteration of the level of consciousness. It is suggested that alpha activity bears close relationship to brain functions which maintain consciousness. Our findings also suggest that alpha activity mechanisms in the cortex and subcortical regions are in close relation, whether or not there may be a reverberating circuit between the cortex and thalamus.

During sleep, anesthesia and hypoxia theta and delta waves appear and disappear in cortical and depth electrograms almost simultaneously. Spiegel *et al.* (1951) reported some cases of petit mal epilepsy in which 3/sec. spike and wave pattern appeared in the thalamic tracing first and from the scalp lead a few seconds later. Knott, Hayne and Meyers (1950) stated that changes of electrical activity of the brain during natural and artificially induced sleep initially appeared in the thalamus and striatum and outlasted the cortical changes. In our cases such a marked difference was not seen. We think that alpha and slow waves in the cortex and subcortical regions are closely related and may represent the state of brain function as a whole.

Natural sleep, trichloroethylene inhalation, subcutaneous Benadryl and scopolamine hydrobromide cause gradual depression of fast activity in the central cortex as well as alpha activity in cortex and thalamus (fig. 10), though the fast activity shows transient slight increase of amplitude in some cases. Intravenous barbiturate, on the contrary, enhances fast activity in the cortical electrogram remarkably. The fast activity persists but is partly masked by large slow waves during ad-

vancing anesthesia. The alternation of the fast and slow patterns during that period indicates a functional shift from waking state to unconsciousness. These findings are similar to those of Hayne *et al.* (1949), Sem-Jacobsen *et al.* (1953, 1955), Bickford *et al.* (1953) and other authors.

Cortical fast activity increases slightly in amplitude and regularity after recovery from barbiturate anesthesia and hypoxia even when alpha activity reappeared in cortical and subcortical tracings, and the subjects show slight euphoria in this stage. These facts suggest that cortical fast activity is not of primary significance in maintenance of consciousness but rather modifies the state of consciousness.

In concluding this report, the authors propose a hypothetical explanation of electrographic changes in the cerebral cortex and deeper structures during various kinds of alteration of consciousness as follows. In the stage in which cortical fast activity shows some change but alpha activity persists in cortex and thalamus and the subject is awake, function of the cerebral cortex is chiefly affected. From the stage in which alpha activity disappears and is replaced by slow waves of 4 to 7/sec. to the stage of spindle burst, the subject cannot percept his surroundings subjectively but can be awakened readily by appropriate stimuli. In such a stage function of cortico-diencephalic system may be affected. Finally in the stage in which large delta waves predominate in cortical and depth electrograms and even strong stimulus can hardly awaken the subject, the lower part of the brain — caudal hypothalamus or midbrain — is also affected. It seems unreasonable to divide anesthetic drugs into cortical and brain stem anesthetics schematically. Effect of various anesthetic drugs on the central nervous system may be analyzed more clearly from the view point such as mentioned above.

SUMMARY

At the time of stereoencephalotomy, electrograms of the central cortex, subcortical white matter and diencephalic nuclei were recorded together with scalp EEG and effects of several anesthetics and hypoxia on the cortical and depth electrograms were investigated in relation to the neural mechanism underlying alteration of consciousness.

The investigations were carried out on patients with neurological disorders, those being chosen with normal or near normal EEGs.

1. Augmentation of cortical fast activity by intramuscular thiopental sodium was not so remarkable as that caused by intravenous administration. After an initial stage of slightly increased voltage and duration, amplitude of cortical fast activity gradually decreased. Alpha activity in cortical and subcortical regions also disappeared and was replaced by slow waves of around 6/sec. In several minutes spindle bursts appeared in all leads. When the subject was awakened slight increase in the voltage of cortical fast activity persisted for a while, even though alpha activity reappered in cortical and subcortical regions. Electrographic changes by rectal chloral hydrate were similar to those by intramuscular barbiturate.

2. Inhalation of trichloroethylene caused gradual depression of cortical fast activity and substituted 4 to 7/sec. slow waves for alpha activity. Gradual depression of cortical and subcortical electrograms was also shown by subcutaneous and intravenous Benadryl with little augmentation of cortical activity.

3. Inhalation of pure nitrogen gas developed an initial depression of cortical and subcortical activity followed by a period of increased voltage and duration. Cortical fast activity showed gradual slowing and enhancement with advancing hypoxia. Loss of consciousness was almost coincident with appearance of delta waves in the cortex and depth. After the recovery of consciousness the fast activity tended to remain augmented.

4. From the findings on the clinical and electrographic effects of anesthetics and hypoxia, it is suggested that alpha activity mechanism is closely related to maintenance of waking state. Changes of cortical fast activity, on the other hand, have no primary significance for wakefulness or loss of consciousness but rather modify the state of consciousness. Neural mechanism underlying alteration of consciousness was discussed from this view point.

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CORRELATION OF RHINENCEPHALIC ELECTROGRAMS WITH BEHAVIOR

A Study on Humans Under the Influence of LSD and Mescaline

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Correlation of behavioral changes with scalp electroencephalograms has been notably unrewarding, although it is difficult to imagine that such behavioral changes could occur without distinct electrophysiologic manifestations in the central nervous system. The development of techniques for implanting cortical and subcortical electrodes in humans has offered a considerable refinement in the experimental procedure of establishing such mind-brain correlations (1, 8, 10). Despite the crudeness of both the instrumentation and manipulation by neurophysiologic standards, some attempts at correlations have already been reported in the literature using the electrode implantation technique (5, 19, 27, 37, 45, 46). Thus, Hodes *et al.* found septal spiking in schizophrenics (24); Sem-Jacobsen *et al.*, high amplitude paroxysmal slow waves correlated with hallucinations (47); and Lesse *et al.*, fast spindling activity with emotionally significant memories (28). Further data on correlations of behavior and brain activity have resulted from subcortical stimulation through these same recording electrodes (4, 5, 6, 18, 20, 31). It seemed reasonable, then, that by inducing behavioral changes with drugs we might have a controlled method of correlating behavioral and brain electrographic activity. Preliminary studies have already verified the usefulness of this method, particularly with the barbiturates, reserpine, chlorpromazine, and alpha chloralose (3, 21, 33, 34, 35).

As d-LSD-25 and mescaline most consistently induce behavioral changes characteristic of psychosis, it seemed that it might be particularly fruitful to study the effect of these drugs on the depth electrograms despite the lack of consistent scalp electroencephalographic changes reported in the literature. Inasmuch as many behavioral characteristics of the reaction to these drugs are those of an exogenous or toxic psychosis, particularly the distorted perceptual symptoms and illusory phenomena, it is surprising that there is not more cortical involvement revealed by the electroencephalogram. However, the clouding of sensorium and memory loss characteristic of the classic toxic psychosis is lacking, and other symptoms, particularly bodily distortions, feelings of depersonalization, and vague referential paranoid ideas, are more suggestive of early schizophrenia, a disease with a noticeable lack of characteristic scalp electroencephalographic patterns (22, 23). The change, usually induced by these drugs on the scalp electroencephalogram is characterized by the disappearance of the alpha activity apparent in the relaxed record, with the subsequent appearance of beta activity characteristic of tension (41, 42). However, a recent report by Bercel *et al.* (2) suggests that even the scalp recordings may be of more significance than merely reflecting an increase in tension. In his 25 patients, 7 showed an increase rather than a decrease in the alpha index. The beta activity when noted spread slowly from the central (Rolandic) region to other areas, rather than appearing simultaneously throughout the cortex with the disappearance of alpha as one would expect with alertness or tension. Three of their patients showed paroxysmal activity of 6 per sec. bursts in all leads; and 4, paradoxical alpha activity. Delay (7) reported that ex-

tremely high doses in rabbits caused complete flattening of the record with the disappearance of the rhythmic element. A more recent study in animals by Schwarz *et al.* (44) indicates that mescaline placed intraventricularly induces paroxysmal activity in the form of 3 to 4 per sec. sharp waves in the temporal region, as well as longer paroxysms of 10 c/sec. beginning in the right frontal-temporal area, spreading to the occipital region, finally involving the whole hemisphere. Schwarz *et al.* (43) in another study with subcortically implanted electrodes in humans showed that mescaline and LSD induced, particularly from the depths of the temporal lobes and the ventral medial region of the frontal lobes, paroxysmal discharges which consisted of 2 to 7 per sec., spike focus in an epileptic patient, and continuous focal high amplitude slow waves from the ventral medial regions of the frontal lobe during pronounced hallucinations. Generally, these responses were reversed by chlorpromazine. Thus, it seems definite that paroxysmal activity occasionally can be induced on the surface of the cortex and in the isocortex by mescaline and d-LSD-25. The authors felt that extensive subcortical recordings might reveal more consistent electrophysiologic abnormalities than have been found with cortical or scalp recordings.

In this study we recorded not only from isocortex but also from the deeper juxtallocortical, allocortical, and diencephalic structures in humans whose behavior was altered by the administration of d-LSD-25 and mescaline, after first establishing careful behavioral and electrographic baselines. The rationale and theoretical considerations which determined the electrode placement have been previously reported (17). As a further check, attempts were made to reverse the behavioral changes by using reputed blocking agents such as Frenquel (alpha-piperidyle-diphenyl carbinol hydrochloride), chlorpromazine, and reserpine. The behavioral changes and electrographic changes were compared with those induced by alpha chloralose, which has already been shown to induce both cortical and subcortical hypersynchronous activity (34, 35).

METHOD

Six patients who had subcortical and cortical electrodes implanted by the stereotaxic method, augmented by ventriculography (1), were used in this study.[1] These were chronically ill patients who had not responded to known therapeutic measures, the subcortical electrodes being implanted for therapeutic purposes, namely, electro-stimulation (17). Table I is a summary of the drug experiments. It will be noted that 4 of the 6 patients were unquestionably schizophrenic; one was diagnosed an acute schizophrenic, although there was a question of psychomotor epilepsy, and one suffered from paralysis agitans. Fourteen studies were done with d-LSD-25, ranging in doses from 50 to 200 μg. There were 9 attempts to block the d-LSD-25 reaction, 6 with Frenquel, one with reserpine, and 2 with chlorpromazine. Two studies were done on 1-LSD-25, 6 with 400 to 500 mg. mescaline either by mouth or intravenously, and 2 attempts were made to block the mescaline reaction, once with Frenquel, another with chlorpromazine. These data were compared with the results of 5 studies on the same patients receiving 500 mg. alpha chloralose plus ½ mg. scopolamine, details of which have been reported before (34). The locations of the intracranial electrodes were as follows: 21 electrodes resting on the pia-arachnoid over the cortex, 19 in the septal region, 26 in the hippocampus and/or amygdaloid region, 9 in the hypothalamus, and 6 in other areas including the caudate, thalamus, nigra and pallidum.

Details of the technique for implantation described elsewhere will not be repeated here (1). Briefly, in the operating room there was a fixation of the stereotaxic instrument to the patient with ventriculograms taken on a superimposed grid corresponding to the two planes of the stereotaxic instrument. Localization of subcortical areas was determined by relationships to bony structures and air in

[1] This was a multidisciplinary research program under the direction of Dr. Robert G. Heath, Chairman of the Department of Psychiatry and Neurology, Tulane University School of Medicine. The program is supported by the Commonwealth Fund.

TABLE I

SUMMARY OF EXPERIMENTS

Patient	Dx	d-LSD (μgm)	+ blocking agent	I-LSD	Mescaline (mgm.)	+ blocking agent	α chloralose + scopolamine (mg.)	Intracranial Electrodes: Cortex	Septum	Hippo.-Amyg.	Hypo.	Other
A-11	Schiz. Cat.	100 50 100	 Frenquel 50 mg. t.i.d. Frenquel 50 mg. t.i.d.					L.Front	R.Ant.	R.A.Amyg. R.P.Amyg. R.A.Hippo. R.P.Hippo.	L.Post.	Caudate
A-12	Schiz. Par.	80 200			400 P.O. 500 P.O.		500 + ½	R.&L.F. R.&L.Par.	R.&L.A. R.&L.P.	R.&L.A.Amyg. R.&L.P.Amyg.		
A-16	Schiz. Heb.	100					500 + ½	R.&L.F. R.&L.Par.	R.&L.A. R.&L.P.	R.&L.Hippo.	Ant. Post.	
		100	Frenquel 80 mg. t.i.d.					*	Left R.A.&P.	R.&L.Hippo. R.Amyg.	R.&L.	Caudate, Thalamus
A-19	Schiz. Simple	50 50	 Frenquel 20 mg. t.i.d.	100	500 I.V.		500 + ½	L.Front. L.Temp. R.Occip. R.Par.	L.Ant. L.Post.	2 R.&L.A.Hippo. 2 R.&L.P.Hippo. R.Amyg.		Caudate
A-21	Schiz., Ac. ?Psycho-motor	100	Frenquel 100 mg. I.V.		500 I.V.		500 + ½	R.&L.Cor. R.A.&P.T. L.A.&P.T.	R.A.&P. L.A.&P.	R.A.&P.Hippo. L.A.&P.Hippo. R.&L.Amyg.	R.A.&P.	2 Ant. Thalamus
A-22	Paralyses Agitans	100 100 100 100	Reserpine 10 mg. I.V. chlorpromazine 50 mg. q.i.d. chlorpromazine 100 mgm. I.V. Frenquel 100 mgm. I.V.	1,000	500 I.V. 500 I.V.	Frenquel 100 mgm. I.V. chlorpromazine 50 mg. q.i.d.	500 + ½	L.Front. L.Par.	Post.		R.Ant. R.Post.	R.A.&R.P.Thala. R.A.&R.P.Nigra R.A.&R.P.Caudate L.A.&L.P.Caudate L.A.&L.P.Pallidum
Total	6 patients	14-d-LSD	9 blocking	2 I-LSD	6 Mescaline	2 blocking	5 chloralose	21	19	26	9	16

* Two operations with electrode placement.

the ventricles. Placement of the electrodes was checked during the operative procedure and repeatedly throughout the studies. There were no changes in position of these electrodes except for patient A-22. This occurred after the present studies had been completed. The two most significant areas for this particular study were the septal and hippocampal-amygdaloid regions. The septal region has been defined by Heath as follows (16): The caudal border of this area is the anterior commissure; the rostral extent, the tip of the anterior horn of the lateral ventricles. Medially the border is the midline space separating the hemispheres, while dorsally the border is the septum pellucidum proper and the base of the lateral ventricle. Ventrally, the area extends to the base of the brain, and laterally, it extends about 5 mm. from the midline. Thus, it includes in whole or part the subcallosal gyrus, rostrum of the corpus callosum, olfactory tubercle, septal nuclei proper, subcallosal fasciculus, pyriform cortex, and various olfactory pathways. Although physiologically and anatomically the amygdaloid and hippocampal regions are separate entities, because of the difficulties determining in some instances whether electrodes were definitely in the hippocampus rather than in the amygdala, they have been grouped together. The main landmarks used for determining this region were the rostral tip and caudal aspect of the temporal horn of the lateral ventricle.

Following the operative procedure, a period of 2 weeks to one month was allowed for the electroencephalogram to return to the baseline, as the trauma of electrode placement usually induced focal slow wave activity which subsided during this waiting period. All the patients had extensive psychiatric, neurologic, and psychologic work-ups as described elsewhere (17). For extended periods prior to the studies reported here, their behavior was followed closely on the wards, during electrographic recordings, and on visits outside the hospital.

The recordings were made on the standard 8-channel Grass machine using both monopolar and bipolar methods. On some occasions, two 8-channel machines were synchronized to give a 16-channel recording. Both scalp and intracranial electrograms were made in all instances with and without the use of muscle filters. A baseline recording was made before each test, and the recording continued until the drug effect reached its peak. Follow-ups were then made for 15 to 20 min. periods, 4 to 6 hours after the previous recording. On selected occasions, an Offner frequency analyzer was used. This was calibrated with the aid of a standard oscillator and oscilloscope which gave the appropriate Lissajous figures. The drift in analyzer was 0.1 per cent after a 3-hour warm-up. Our machine was stable enough so that weekly calibrations proved sufficient. The patients rested on a comfortable bed in a large, air-conditioned, sound-attenuated room, with all instrumentation and technical assistants in an adjoining room, where a large one-way mirror allowed constant observation of the patient. A 2-way speaker system made it possible to hear spontaneous productions of the patient or to talk to the patient without entering the room. At the time of the baseline recording, a brief mental status examination was done. This was particularly oriented towards determining attitudes about the present study, feelings towards the examiner, basic affect, and immediate ideation, particularly as regards the presence of hallucinations or delusions. Sensorium was checked in some detail. At one-half hour intervals during the experiment the sensorium was re-checked and the patient was asked about subjective changes without resorting to leading questions. The meaning of overt changes in behavior was discussed. During the baseline and at 15 min. intervals after the patient received mescaline or d-LSD, he was told to close his eyes. The examiner pressed lightly on his eyeballs asking what he saw. The flashing lights induced were often perceptually distorted into visual hallucinations. After the experiment was over, the patient was directly questioned about subjective changes, such questions being: "Have you ever had these feelings before ? Did the room change in apparance ?" etc. Positive responses to these direct questions were eva-

luated carefully as we were well aware of the suggestive element of subjective changes. Behavior was followed closely for the next 24 hours. There was always a period of at least 36 hours between the experiments with different drugs, and in some instances subsequent studies were delayed as long as a week because of the persisting effect of the previous experiment.

RESULTS

Individual responses

A-11. This patient was a 31-year-old mute, manneristic, catatonic schizophrenic who had been psychotic for the previous 10 years. Although untidy, he did take care of his personal needs. He had not responded with clinical improvement to EST, Frenquel, reserpine, or chlorpromazine. Since he was inaccessible for the usual psychiatric testing, it was difficult to ascertain what subjective effect, if any, 100 μg. d-LSD-25 had on this particular patient. The afternoon and evening following the administration of the drug, he was more negativistic, refused to feed himself, and would not cooperate for follow-up studies.

Electrograms showed only a decrease in the small amount of alpha present in the baseline and some increase in the beta activity on the cortex as well as in the caudate area (fig. 1). During a period of 4 hours there were 3 episodes of paroxysmal 6 per sec. waves coming from all leads, with highest amplitudes located in the hippocampal-amygdaloid region. These were of doubtful significance as they occasionally occurred in the baseline recordings. After 19 days' administration of 50 mg. Frenquel three times daily, the response to 100 μg. of d-LSD-25 seemed to be the same as above described, both behaviorally and electrophysiologically. There were still infrequent episodes of paroxysmal activity, but again these were so rare as to be of doubtful significance insofar as having been induced by the drug. As before, the fast activity in the cortex and caudate was noted. Despite Frenquel, he again showed increased negativism the afternoon following the experiment.

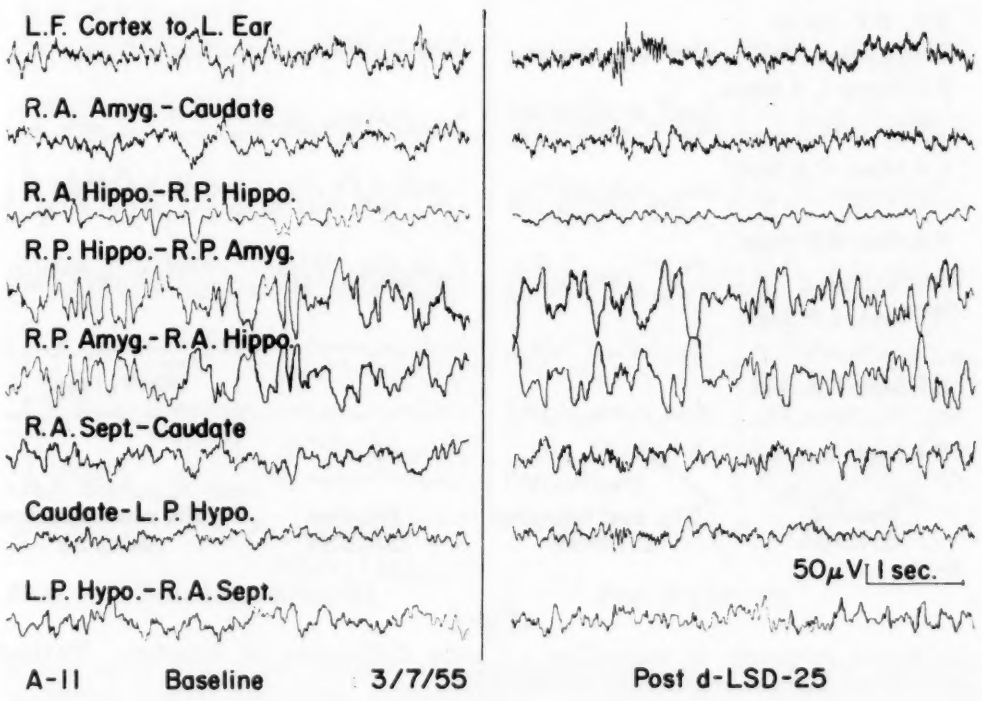
L.F. Cortex to L. Ear
R. A. Amyg. - Caudate
R. A. Hippo. - R. P. Hippo.
R. P. Hippo. - R. P. Amyg.
R. P. Amyg. - R. A. Hippo.
R. A. Sept. - Caudate
Caudate - L. P. Hypo.
L. P. Hypo. - R. A. Sept.
50μV 1 sec.
A-11 Baseline 3/7/55
Post d-LSD-25

Fig. 1

Increased beta, cortex and caudate following d-LSD-25. Similar change while on Frenquel 50 mg. t.i.d.

A-12. This 27-year-old patient was a paranoid schizophrenic who had withdrawn from all social contact and suspiciously evaded

questions about her underlying delusions of persecution. Periodic anxiety and rage attacks made hospitalization necessary, although patient steadfastly denied that she was mentally ill. Her uncooperativeness made an evaluation of either the d-LSD or mescaline reaction difficult. Despite 200 μg. of d-LSD-25, the patient showed little clinical change except for minimal somatic sensations such as numbness in the arm. She was more evasive, at times would laugh inappropriately, all of which she occasionally showed spontaneously. There were no discernible changes in the electrograms, but there was considerable beta activity present in the baseline cortical electrograms.

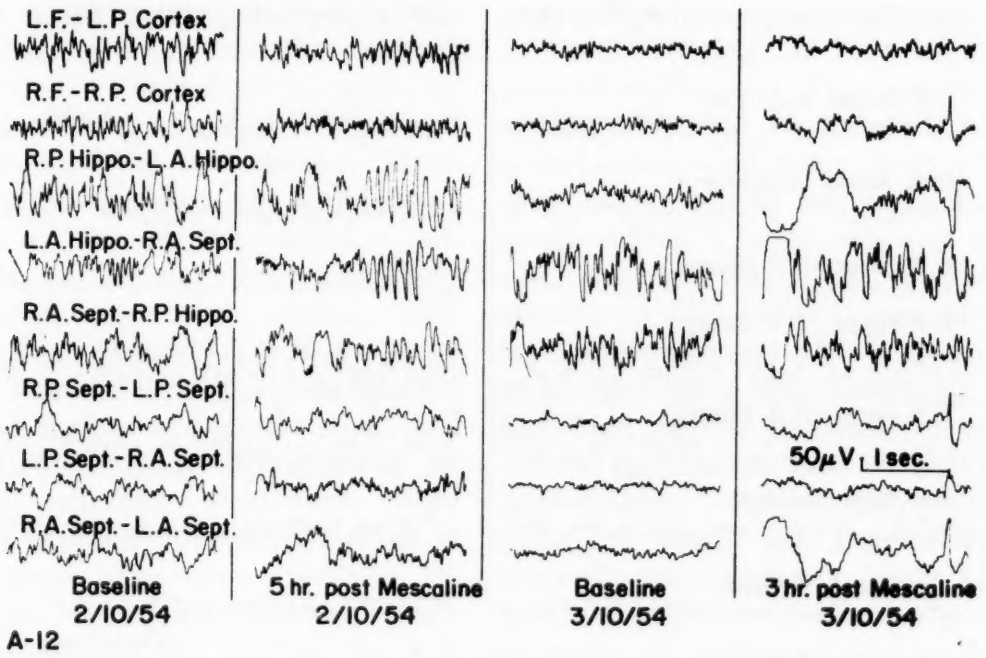

Fig. 2

Different response to mescaline — note difference in baseline. Patient showed no EEG changes with d-LSD-25.

This patient received mescaline on 2 occasions. In both instances the behavioral response was more dramatic. She was more open in expressing her hostility and negativism. In comparison to d-LSD-25, she admitted that this drug made her upset even though she refused to describe her subjective feelings. She did admit to a number of somatic complaints such as nausea, numbness, blurred vision, and headache. Once, the nausea was accompanied by vomiting. The anterior septum, accompanied by sharp high amplitude spikes in the right septal and hippocampal areas reflected also in the right cortex (fig. 2).

A-16. This 33-year-old patient had been psychotic for 10 years. At the time of the present studies, although evasive in certain areas, she was quite loquacious and cooperative, willing to talk about her subjective feelings. Her emotional response was one of bland indifference, inappropriateness, or silly giggling. She was unkempt, dishevelled, rambling, and scattered in her productions. Although not hallucinating, she had a number of bodily

delusions and sexual preoccupations. The behavioral response to d-LSD-25 was dramatic. She said she felt "peculiar", appeared frightened, was extremely restless, writhing in bed as if orgastic. She would reach out, grab or kiss the doctor, then push the doctor away while expressing numerous guilty and expiatory feelings. At the height of this, she had visual hallucinations of "tombstones on the ceiling". The electrograms at the height of the drug effect showed a sharp 8 to 10 per sec. wave followed by a slow 2½ per sec. component coming from the anterior hypothalamus (fig. 3), and occasional sharp spikes from the posterior hippocampus and throughout the septal area. At the same time, there was considerably more high amplitude delta background activity in the septal leads. Beta activity present in the cortical leads during the baseline seemed to be definitely increased, although this is not apparent in figure 3.

Even more dramatically than in the previous studies high amplitude delta activity in the septal region definitely increased. At other times, in both the septal and hippocampal regions there were high amplitude 6 per sec. flat-topped waves lasting for 20 to 30 sec. Also in the hippocampal leads there would be bursts of sometimes 15 per sec., other times 25 to 30 per sec., activity which occurred in occasional baseline recordings and was presumed to be associated with emotionally charged memories (11). The frequency analyzer revealed a definite shift in all deep

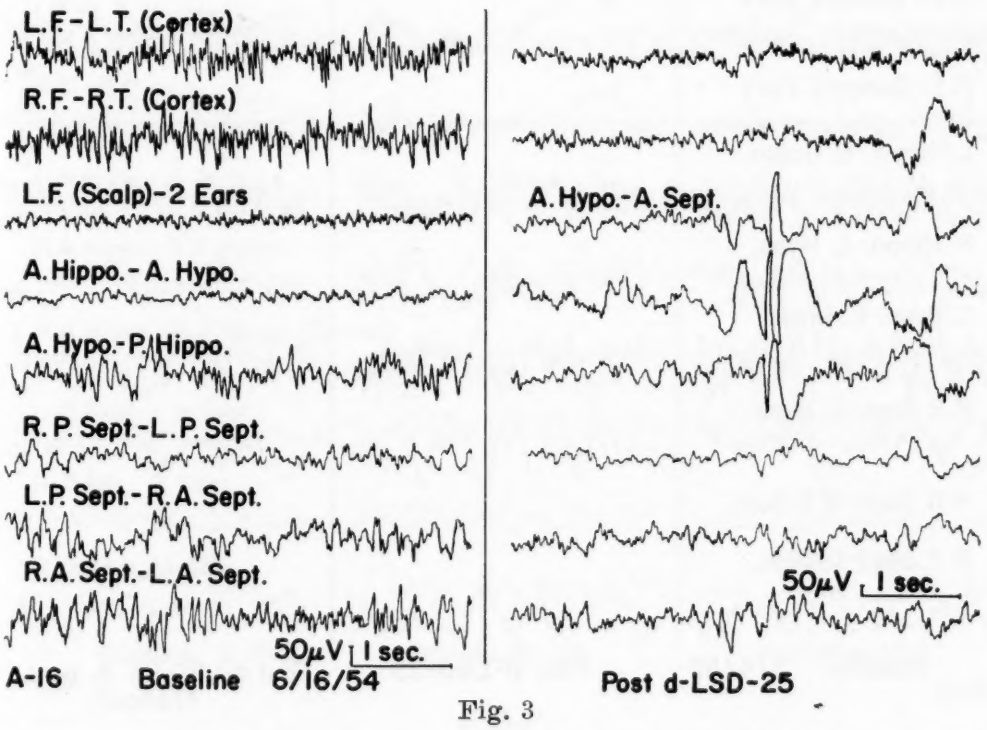

Fig. 3

Sharp wave with slow component from hypothalamus. Spike also occurred in septal region and post. hippocampus. Septal region showed increased delta (not shown in figure).

Nine months later, after a subsequent electrode re-implantation, she underwent a similar study. Although this time she denied hallucinations, her behavior was otherwise similar. leads to the slower wave frequencies, with 5, 6, and 7 per sec. waves present in the baseline virtually disappearing to be replaced by 1, 1½, and 2 per sec. activity.

At the height of the clinical response, the patient was given 80 mg. of Frenquel intravenously. As she had had amytal on numerous occasions in the past to quiet her down, the suggestive effect of such an injection is obvious. In any event, she immediately relaxed. However, there were only minimal changes on the electrograms. The high amplitude delta

activity in the septal region diminished, but the paroxysmal activity continued even though her behavior was considerably better, there being much less agitation with accompanying hyperventilation. The electrographic changes may have been the result of this rather than the direct effect of Frenquel (fig. 4).

A-19. This 28-year-old patient had simple auditory hallucinations of God talking to him and at times calling him accusatory names which rarely would elicit a rage response with destructiveness. Otherwise, he was emotionally flat and isolated, giving the appearance of a mental defective. He either could not or would not give any detailed subjective data. This patient received relatively low doses of d-LSD-25 (50 μg.). His only comment after the drug was that everything "moved fast", by which he meant that his own actions and those of others seemed particularly quick. He did, in fact, appear overactive and more emotionally responsive than usual. He now smiled broadly, although this was a somewhat sheepish, inappropriate grin. Except for the cortex showing a decrease in alpha with an increase in beta activity after both drugs, the only difference in the electrograms was the appearance of high amplitude delta activity with the baseline frequency superimposed, appearing in the septal leads. These slow waves were not associated with sleep. The experiment was repeated on a subsequent occasion after the patient had been on 25 mg. Frenquel t.i.d. for a period of 11 days. Although behaviorally the response was very much the same, this time the slow activity in the septal region was not apparent. On neither occasion did the patient admit to hallucinations. One hundred micrograms of 1-LSD was ineffective clinically, and resulted in no cortical or subcortical electrographic changes.

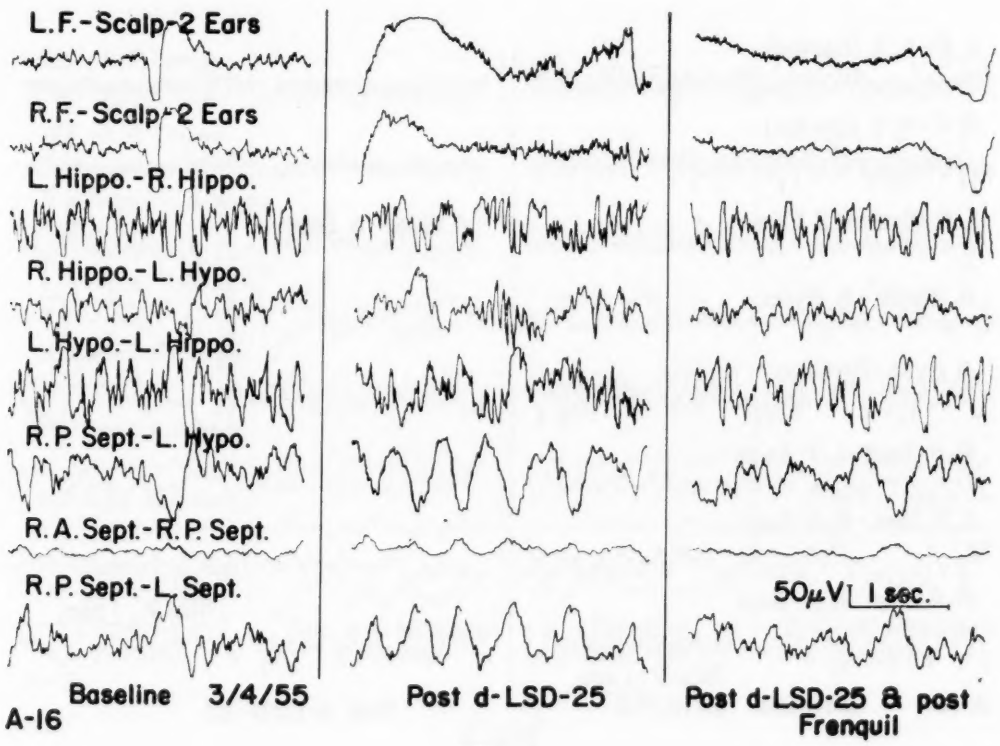

Fig. 4

Slow activity in septum induced by d-LSD-25. Question whether Frenquel responsible for decrease in slow activity.

However, following 500 mg. of mescaline intravenously, there was an immediate somatic reaction of blurring of vision, pain in the shoulder and chest, followed one-half hour later by nausea. He also felt that things were "soft", by which he meant dreamy or unreal. With eyeball pressure, the response was as follows: one-helf hour, he saw only white lights; one hour, these became red and

blue; at one and one-half hours, he suggested that the yellow colors were flowers and the red were Coke machines; at two hours he saw bones, an airplane, a sword, and apples. On this occasion, the high amplitude delta activity appeared only rarely in the septal region. On the other hand, low amplitude diphasic spikes, sometimes followed by low amplitude slow waves, were noted in the hippocampal region (fig. 5).

A-21. This 28-year-old patient required hospitalization because of episodic rage reactions, during which time she would destroy furniture, attack her husband or children with homicidal intent, and at times mutilate or try to kill herself. During these episodes, she was hallucinating, particularly seeing her children and family, as well as hearing them admonish her for her bad behavior. These episodes were often, but not invariably, accompanied by amnesia, and would last from a few hours to a few weeks, being severe enough to require recurrent hospitalizations where she had in the past been treated with EST. These episodic behavioral disturbances were preceded by mounting irritability and occipital headaches. During the intervals between attacks there was demanding, possessive, irritable, and pathologically jealous behavior. At times she was so disorganized that she was unable to care properly for her children or her husband. She had numerous hypochondriacal preoccupations which necessitated frequent trips to the doctor and hospitalization with several laparotomies. On routine scalp electroencephalograms prior to electrode implantation, bi-frontal theta activity was noted but no other abnormality. Baseline deep recordings following electrode implantation showed septal theta activity and an occasional diphasic single spike in the left hippocampal region which was never apparent on the temporal cortex except for one instance when the patient had received Metrazol (21).

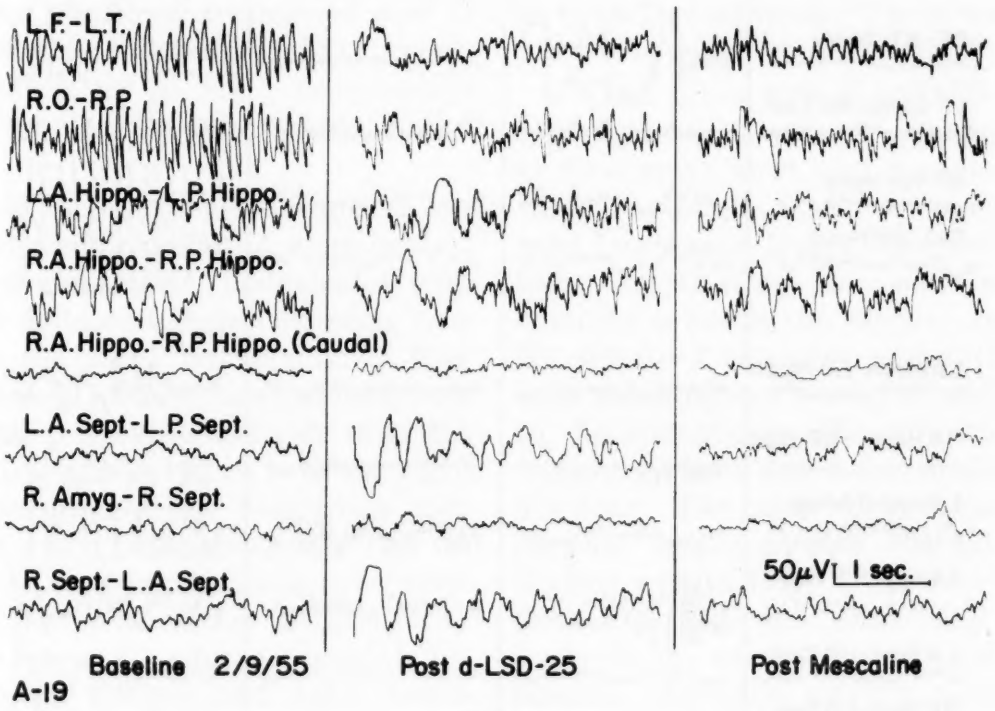

Fig. 5

Slow wave in septum after d-LSD-25 not accompanied by hallucinations. Spiking after mescaline from hippocampus is accompanied by hallucinations.

Figure 6 illustrates the paroxysmal high amplitude bursts of activity in the alpha-theta range appearing in the right hippocampus. The bipolar recording of right anterior hippocampus to right posterior hippocampus showed paroxysms of 6 and 14 per sec. monophasic spikes. Sometimes this paroxysmal activity was seen in the thalamus,

with amplitudes of approximately 5 μV., as compared to the 200 μV. recorded from the right posterior hippocampus. Not shown in figure 6, but noticed in the record, was a considerable increase in the sharp diphasic spikes seen during the baseline in the left hippocampal leads. With mescaline similar activity was induced in the right posterior hippocampus, but the amplitude was considerably less and the paroxysmal bursts occurred rarely as compared with the d-LSD response. Paroxysmal activity did not occur in the septal leads in either instance. In this particular patient, then, although paroxysmal activity was induced by both mescaline and d-LSD-25, the latter induced a much more dramatic effect in the electrograms. This correlated well with the behavioral response. Under d-LSD not only did the patient complain of numerous somatic symptoms, such as nausea, blurred vision, head and back ache, but also she became depressed, cried, constantly struggled to get up, and was completely uncooperative. She showed some dif-

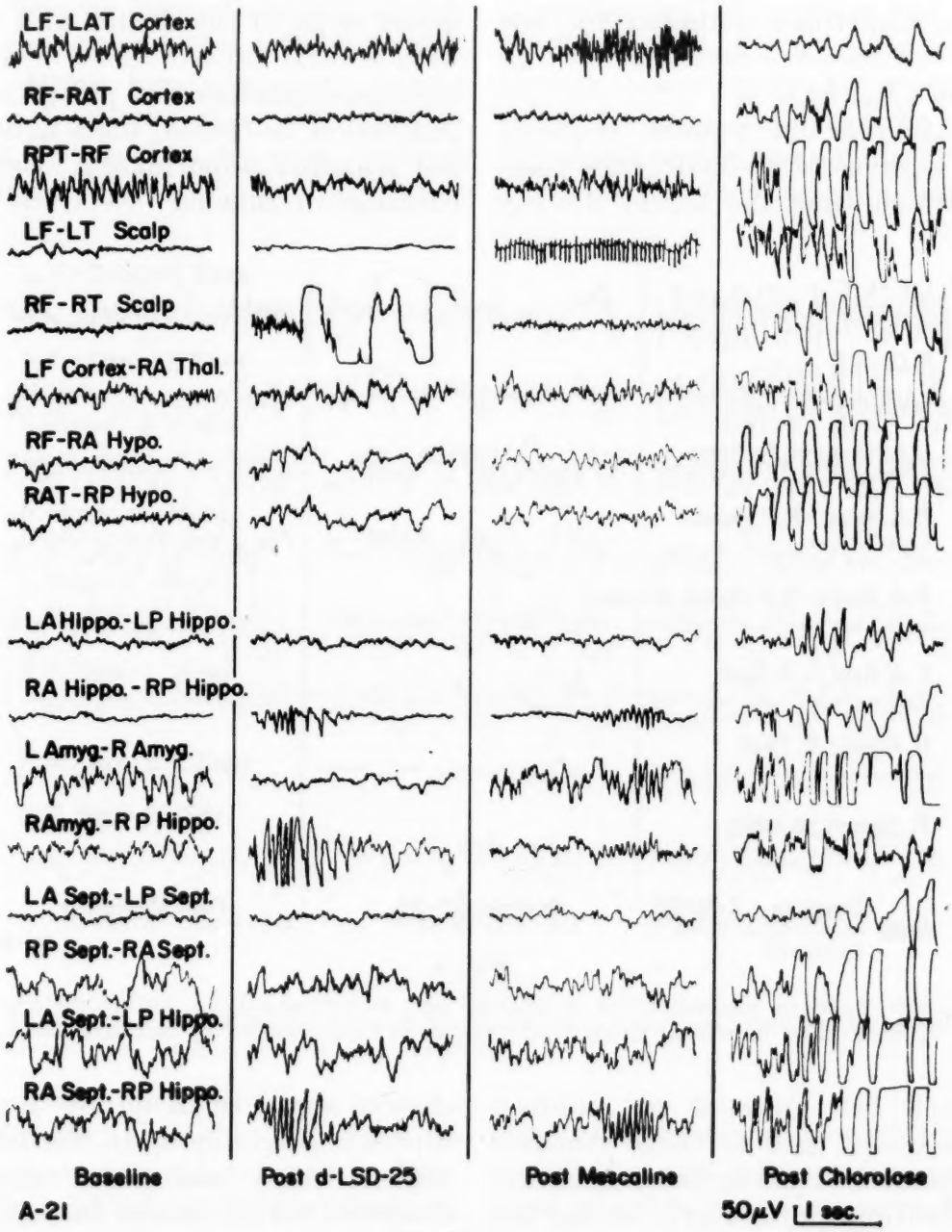

Fig. 6
Paroxysmal activity after d-LSD-25 frequent, but rare after mescaline.

ficulty in remembering the doctor's name, appeared to be in a trance-like state, although her attention was easily obtained, and then she was oriented and in good contact with her surroundings. She overtly expressed rage, complained of feeling as if she was going to have a convulsion, mentioned numerous paranoid referential ideas, and hallucinated her children standing at the foot of the bed. On the other hand, after mescaline, although she again had numerous somatic complaints, such as feeling cold, shivering, difficulty in breathing (purely subjective), and reported sensations that her legs were drawing up (also subjective), there was no marked agitation even though she appeared frightened and at times angry. She had a sensation that "everything was pushing in on me", occasionally cried, but this time had no overt visual hallucinations.

Figure 6 also includes electrograms of her response to alpha chloralose and scopolamine. Here the paroxysmal activity is dramatic, with high amplitude delta and theta occurring predominantly on the right but involving bilaterally both the deep and the cortical leads. At other times, sharp spiking activity was the prominent feature appearing in both the right and left hippocampal areas, sometimes synchronously, but often independently. The behavioral response to chloralose was even more dramatic than that with either d-LSD-25 or mescaline. She became agitated, rageful, began tearing up her clothes, and again hallucinated her children and her husband. The hallucinated children appeared frightened and cringing, while her husband was admonishing her for her rageful behavior. Under chloralose this patient did not show the extensive cortical slowing that some of the other patients did (see fig. 8 and discussion below).

A-22. This was a 48-year-old colored man of low intelligence with only 2 years' education and an extremely impoverished socioeconomic background. Because of this, an adequate medical history was difficult to obtain. Apparently, 6 months before hospitalization a marked tremor was noted in the right hand for the first time. On admission to the hospital, the tremor included not only the right hand but the whole right upper extremity with a slight tremor in both legs, all disappearing with activity and sleep. Cog-wheel rigidity was noted in the right wrist. A mask-like facies and slow voluntary movements were present. Other physical, neurologic, and laboratory studies were within normal limits. There was no history of trauma, vascular accident, or infectious disease prior to the onset of the tremor, although 5 to 6 years previously there was a personality change and the patient was no longer able to hold a steady job, was frequently preoccupied, and complained of difficulty in hearing. Routine scalp EEG's prior to electrode implantation showed S2 activity in both frontal leads. There was a slight amplitude asymmetry in the parietals.

When given both d-LSD-25 and mescaline (on separate occasions), the patient became at first more alert and responsive, then confused, agitated, and uncooperative, with a wild frightened look. Whereas before he had been ingratiating, he now would express hostility towards the doctors and technicians. He sat up frequently and talked to himself as if thinking out loud, but did not appear to be hallucinating. He admitted to feeling frightened and asked for medicine to relieve his fear. The same behavioral and electrographic response was elicited on all four studies with d-LSD-25 and two studies with mescaline. One saw first (and most dramatically in the cortical leads) a decrease in the baseline rhythmic activity which in this patient included alpha and theta frequencies, with a subsequent appearance of low amplitude beta. Somewhat later, paroxysmal waves of a frequency of 10 per sec., occurring in bursts of 3 to 6 waves, appeared in the septal leads. Sometimes these would occur singly, appearing like slow spikes. Occasionally a slow spike would appear in the caudate synchronously with this activity. No paroxysmal activity occurred in the thalamus, substantia nigra, or pallidum. This patient did not have electrodes in the hippocampal-amygdaloid region.

The optical isomer of d-LSD-25 (l-LSD-25) is reported to have no clinical effect. Despite the fact that this patient received

1,000 μg. by mouth, which is 10 times the effective dose of d-LSD-25, no electrographic or behavioral changes were noted.

A number of blocking agents were tried with this patient while he was under the influence of both d-LSD and mescaline. Frenquel, 100 mg. intravenously, did not alter the behavior nor were there any significant changes in the electrograms (see fig. 7). One hundred mg. of chlorpromazine injected intramuscularly at the height of the drug effect of d-LSD-25 did not alter the behavior or the electrograms in the next hour and a half. However, early in the afternoon he became quiet and no longer required restraints, which had been necessary during the previous experiment with d-LSD alone, until late in the evening. Because of this delayed effect, he was next placed on chlorpromazine 50 mg., 4 times a day for a period of one week and then tested on d-LSD-25 and mescaline on separate occasions. Although he would appear somewhat restless, the reaction was much less severe than previously encountered. He always remained cooperative. There was a definite difference in the electrograms. The rhythmic theta activity continued throughout the recording (fig. 7), although there were rare periods when this would disappear and the fast beta activity on the cortex and occasional paroxysmal activity in the septal area was seen. On another occasion, at the height of the d-LSD-25 reaction, the patient was given 10 mg. reserpine intravenously. The electrograms were followed for the next hour and a half without significant change. There was no significant change in behavioral response during the next 24 hours as compared to the d-LSD-25 response without reserpine.

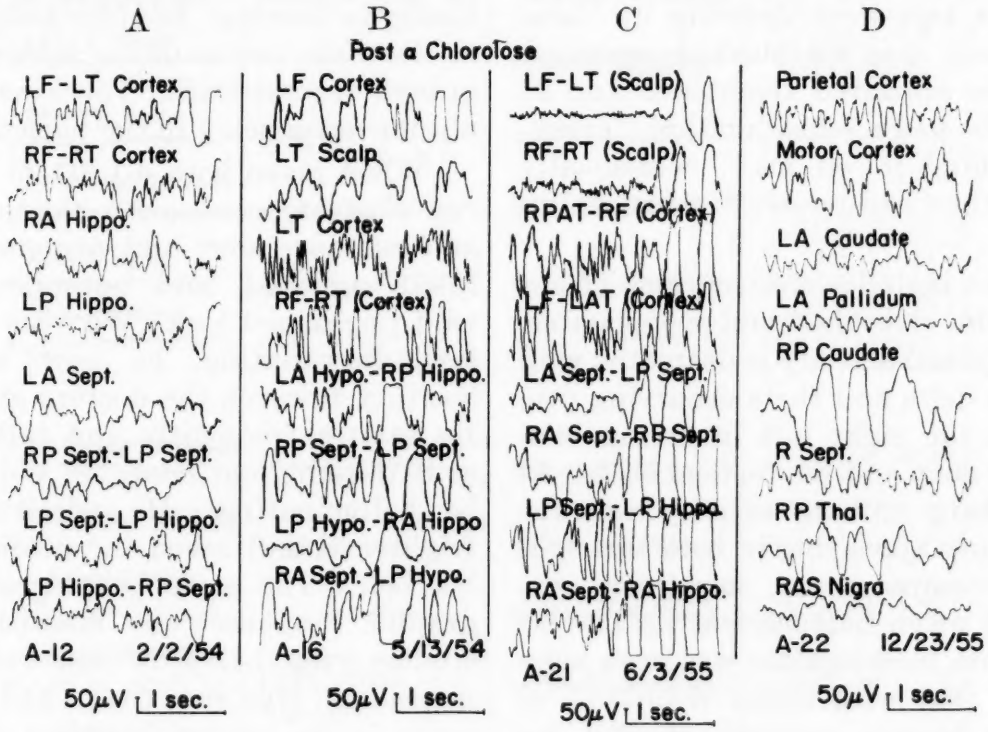

Fig. 8

Response of different patients to chloralose: A — sleepy and relaxed, B — organic confusion, C — hallucinating, D — focal slowing in patient with CNS damage (see text for discussion).

Comparisons between patients

All electrograms, with one possible exception, revealed some response to both d-LSD-25 and mescaline. The generalized response occurred predominantly in the cortical leads; that is, there would be a disappearance of the alpha activity characteristic of the resting record and an increase in the fast activity in the beta range. If there was rhythmic theta activity or underlying delta, this would also decrease in the cortical leads to be replaced by the fast beta. Subcortical activity, particularly from the caudate, amygdaloid-hippocampal,

TABLE II

ELECTROGRAM AND BEHAVIORAL RESPONSE

Patient	d-LSD-25		Mescaline		Blocking Agent		α Chloralose	
	Electrogram	Behavior	Electrogram	Behavior	Electrogram	Behavior	Electrogram	Behavior
A-11	cort. beta no subcort. change except beta	slight increase in negativism			Frenquel no change	did not block drug effect		
A-12	baseline tension no change cort. or subcort.	slight increase in negativism	*parox.* in septum & hippo.	somatic symptoms open hostility			parox. deep cort. slowing	sleepy
A-16	cort. beta sept. slow *parox.* sept., hypo., hippo.	agitated, erotic, guilty, hallucinates			Frenquel less slow in the septal region	quiet, coop.	parox. deep cort. slowing	disorientation memory loss, perseveration, amnesia
A-19	cort. beta no change deep	over active	*parox.* hippo.	somatic symptoms hallucinations	Frenquel no change	did not block drug effect	parox. deep cort. slowing	relaxed
A-21	cort. beta *parox.* hippo.	somatic symptoms emotional lability agitation hallucination	cort. beta rare *parox.* hippo.	somatic symptoms perceptual changes restless	Frenquel no change	did not block drug effect	parox. hippo. no cort. slowing	emotional lability agitation hallucinations
A-22	cort. alpha cort. beta *parox.* septal	agitated uncoop. talked to self	cort. alpha cort. beta *parox.* septal	agitated uncoop.	Frenquel no change chlorpromazine back to baseline	did not block behavior back to baseline	parox. rt cort. & caud. reflecting CNS damag. genl. slowing	sleepy relaxed

and septal areas, would often show similar change, that is, a decrease in amplitude and increase in the fast activity. This is similar to the response found by Schwarz (43), that the amplitude of subcortical activity is diminished under the influence of d-LSD and mescaline. Three records were analyzed by an Offner frequency analyzer. This showed that even when fast activity appeared in the subcortical areas, there was a shift in the background activity to the slower frequency bands. A record that might show 5, 6, and 7 per sec. activity before d-LSD-25 or mescaline, would now show more 1, 1½, and 2 per sec. activity. from background activity, not only because of the wave form, but also because this activity appeared in bursts of one to 10 or more seconds duration. It consisted of the following wave forms and frequencies: 6 to 10 per sec. rhythms lasting for 3 sec., short bursts of high amplitude delta, slow spikes or sharp waves, high amplitude sharp waves followed by a slow component, low amplitude diphasic spikes alone or followed by low amplitude slow component, and monophasic spikes. The wave forms described here were similar to those reported by Hodes *et al.* (18, 24) for schizophrenic patients. All of the schizophrenic

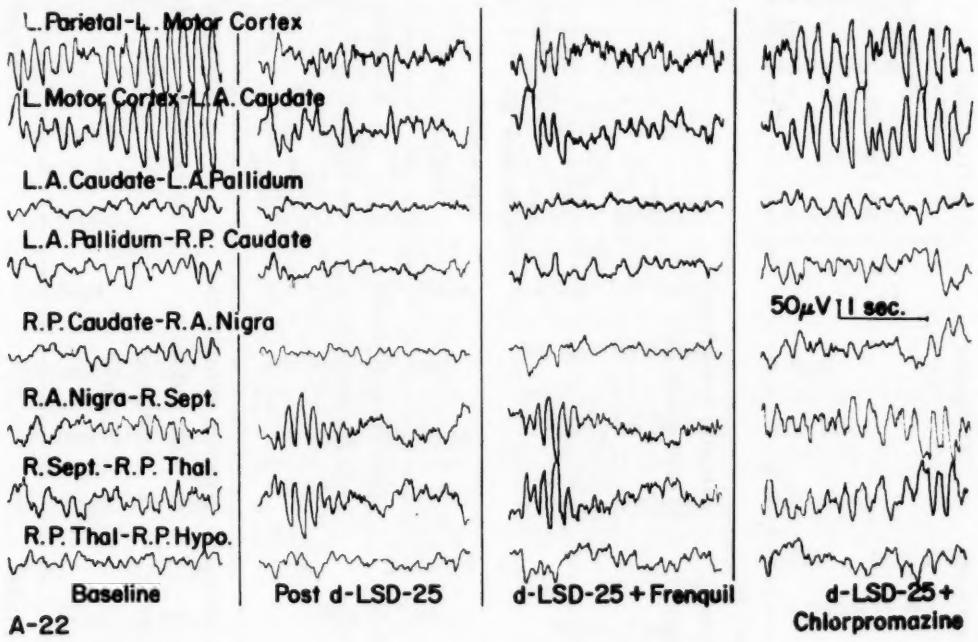

Fig. 7

Decreased cortical alpha and paroxysmal septal activity after d-LSD-25. No change with Frenquel. Return to baseline with chlorpromazine.

This was particularly true of the septal and hippocampal-amygdaloid recordings.

The most significant response to d-LSD and mescaline was the appearance of subcortical paroxysmal activity. This occurred in every patient except A-11, and even in this patient there was suggestive evidence of rare paroxysmal activity. Such activity was most often limited to the septal, anterior hypothalamic, or amygdaloid-hippocampal regions. Table II shows that the paroxysmal activity often did not occur with both drugs. This paroxysmal activity was easily distinguished patients (patient A-22 the exception) had similar wave forms in their waking and/or sleeping baseline recordings. However, the difference in the recordings when the drug was effective was striking because of the paroxysmal bursts of such activity, the unquestionable increase in amplitude of the waves, as well as an increase in the amount of these waves.

Despite the fact that three of the patients, A-11, A-12, and A-22, were chronically ill people who were either unable or unwilling to be subjective reporters, all 6 patients

definitely showed behavioral changes indicating that the drugs were clinically effective. However, there was a wide range in behavior, from mere anxiety to hallucinating psychoses. In those patients who simply showed a decrease in the rhythmic alpha or theta activity of the cortex and an increase in the beta, the behavioral responses were not marked and seemed indicative of increased tension. Such instances would be patients A-11, A-12, and A-19, under d-LSD-25. However, the latter two did show more dramatic behavioral changes under mescaline with accompanying paroxysmal subcortical electrographic activity.

The converse was true of patient A-21. Although mescaline did induce rare paroxysmal activity, there was a marked contrast between the frequency of these paroxysmal bursts as compared with the response under d-LSD-25 where the paroxysms occurred at 10 sec. intervals. Again there were corresponding differences in behavior. With the d-LSD-25 the patient was considerably disturbed and hallucinated; while under mescaline, although restless, the response was much less dramatic. Patient A-22 showed paroxysmal activity with both drugs, and became equally disturbed on both occasions.

As the more dramatic behavioral changes were also accompanied by somatic symptoms, particularly aches and pains, blurring of vision, dizziness, shivering, nausea and vomiting, one might say that the paroxysmal activity was correlated with the somatic symptoms. This seemed to be true in most instances but would not necessarily preclude the conclusions of the preceding paragraph. In one patient, A-21, the somatic symptoms were equally marked under both mescaline and d-LSD, yet under mescaline, there was minimal paroxysmal activity in the depth electrogram; so that correlation between somatic symptoms and paroxysmal electrograms appears less likely.

We next checked our results by using blocking agents to alter the behavioral response, while noting any corresponding changes in the electrogram. The only blocking agent extensively studied was Frenquel (alpha-piperdyle-diphenyl carbinol hydrochloride) which was tried in 6 instances on 5 patients under the influence of d-LSD-25 and in one instance on a patient under the influence of mescaline (table I). Unlike the electrographic effects obtained in rabbits by Rinaldi *et al.* (40), we found only questionable electrographic change in our human subjects. This corresponded with the questionable behavioral changes. In most instances, there was no lessening of the d-LSD or mescaline reaction whether Frenquel was given as 100 mg. intravenously during the experiment, or in 20 to 80 mg. doses t.i.d. for several weeks prior to the experiment. In one instance, there was a dramatic clinical response to Frenquel (patient A-16). In view of the lack of response in the other patients, we interpret this change as resulting from suggestion, inasmuch as the patient previously had had frequent intravenous injections of amytal to alleviate her agitation. Figure 4 shows the disappearance of the high amplitude delta activity in the septum after Frenquel. As there was overbreathing during the height of the LSD response, it is questionable whether the disappearance of the high amplitude delta might not be due to the lack of hyperventilation rather than to any direct effect of Frenquel itself. However, one other patient, A-19, without showing behavioral changes, did show less septal slow activity after Frenquel. The only consistent blocking effect was noted with chlorpromazine, although our studies with this drug were limited to 3 experiments on one patient, A-22. Two studies were done after the patient had been receiving chlorpromazine 50 mg. 4 times a day, for a period of at least a week before administration of d-LSD or mescaline. In contrast to the previous studies without chlorpromazine, the patient showed only slight restlessness and occasional lack of cooperation because of his confusion. The electroencephalographic response paralleled this difference in behavior. Figure 7 illustrates the blocking effect of chlorpromazine and contrasts it to the lack of blocking effect, as far as electrograms are concerned, with Frenquel. The EEG response induced by d-LSD and mescaline alone, which has been described

above, occurred only rarely when the patient had been on chlorpromazine.

Ten mg. of reserpine given intravenously on one occasion to patient A-22, with the record followed for the next hour and a half and the behavior for the next 24 hours, showed no effect either on the electrograms or in behavior.

As a further check on whether the paroxysmal activity in the hippocampal-septal region was correlated with psychotic behavior, the findings with d-LSD and mescaline were compared with alpha chloralose studies done on 5 of the 6 patients. These studies have already been reported in a previous communication (34). In summary, it has been found that 500 mg. of alpha chloralose and ½ mg. scopolamine, although used clinically as a sedative, elicits paroxysmal hypersynchronous activity in patients with a history of epilepsy or central nervous system damage. Also, it was found that in many psychiatric patients, particularly those who showed behavioral disturbances in the past, paroxysmal hypersynchronous activity could be induced, and when this occurred there were oftentimes dramatic changes in behavior simulating the spontaneous behavioral disturbances that led to the patient's hospitalization. Consequently, it was felt that if alpha chloralose would induce the paroxysmal changes in the hippocampal and septal region as LSD and mescaline had, and if these were accompanied by similar changes in behavior, it would further support for our thesis that paroxysmal activity in the hippocampal-amygdaloid and septal regions is correlated with psychotic behavior. We found that if, as in patients A-12 and A-19 (table II and fig. 8), the paroxysmal activity was minimal but the generalized slowing predominant, one was most likely to see relaxed, sleepy behavior. However, if generalized paroxysmal high amplitude delta activity was present, such as that shown by patient A-16, the response was more likely an organic confusional state with disorientation, memory loss, perseveration, amnesia, accompanying any manifest disturbance in behavior. On the other hand, if, as the case of patient A-21, high amplitude paroxysmal activity occurred in the septal-hippocampal region with only slight paroxysmal activity reflected in the cortex and little generalized slowing, the response was similar to, if not even more dramatic than, d-LSD and mescaline. With chloralose and scopolamine this patient showed some slight confusion and slowness in performing simple intellectual tasks, but she never became disoriented. She did become extremely agitated, hallucinated her children, talked with the hallucinations, and struggled to get away from them. The same patient in a repeat chloralose study at a later date showed less deep paroxysmal activity with more generalized slowing in the cortex. At that time she did not hallucinate, was not nearly as agitated, but did become more confused. It would seem, then, that if paroxysmal activity is induced in the septal, hippocampal-amygdaloid region without dramatically affecting the cortex or being accompanied by generalized cortical slowing, the behavioral changes are more marked, while the clouding of sensorium and disorientation is minimal.

DISCUSSION

The important question to ask at this point is whether these findings shed further light on the brain mechanisms in psychotic behavior. Heath (16) points out that the septal region is part of the olfactory system which anatomically would appear to be a correlating structure interposed between the higher neocortical levels and the diencephalic and mid-brain structures. The known connection between the septal region and hippocampus was originally responsible for our interest in subcortical recording from the region of the hippocampus and amygdala. Ablation and stimulation studies on animals imply that these areas are important for such diffuse functions as olfactory-gustatory, metabolic, autonomic, and socio-emotional (38). However, similar studies in humans are infrequent. Heath *et al.* (20) report that in stimulation of the amygdaloid nucleus a rage or fear response is induced without impairment of awareness and that this strong emotional response is conscious as well as integrated into the thinking of the patient. Chapman *et al.*, stimulating the

amygdaloid nucleus in four patients, produced feelings of fear, with only momentary confusions and unresponsiveness, although ability to perform skilled acts seemed to be impaired (6). Others (13) have emphasized the automatism, confusion, and unresponsiveness, with amygdaloid stimulation. Freeman (14) reports that the removal of the amygdaloid nucleus in a psychotic patient with intractable hallucinations led to the cessation of the hallucinations following the procedure. In view of the established anatomical and physiological connections between the temporal lobe and the rhinencephalon (48), studies on temporal lobe epilepsy are pertinent for the problem at hand. It has been noted how frequently automatisms of temporal epilepsy are accompanied by emotional auras, particularly intense fear, as well as the fact that in at least some instances the ictal behavior is not associated with obvious alterations in consciousness (29). Gastaut (15) in his classification of psychomotor epilepsy points out that "hippocampal psychomotor epilepsy" is characterized by obvious interictal clinical manifestations which are marked by character and behavior disturbances. Studies from our own laboratories (11,12) point out the frequency of episodic psychotic behavior in a group of patients with temporal spikes as well as persistent and severe disorganizations of the personality which would suggest a diagnosis of "functional psychosis" in over 80 per cent of the patients studied. The difficulties in differentiating ictal from non-ictal behavior suggest a continuity in the clinical picture probably also reflected by a continuity of the physiologic process. Our present studies on LSD and mescaline suggest that paroxysmal electrophysiologic abnormalities can exist within the rhinencephalon without reflection on the corticograms, hence may be a concomitant of psychotic behavior in many patients now diagnosed as suffering from the so-called "functional" disorders because they lack characteristic seizural abnormalities as recorded by scalp electroencephalogram. In fact, reasoning within the psychoanalytic framework, Menninger (30) suggests that nosologically there is a "third order of pathology" standing somewhere between neurosis (second order) and the psychoses (fourth order), which he calls "episodic dyscontrol". These orders represent hierarchically successive groups of control devices that the total organism uses in its adaptation to stress. In this third order there is an episodic "ego failure", variously diagnosed as psychopathic behavior, convulsions, catathymic crises, some schizophrenic reactions, manic attacks, hysterical dissociation, etc. Thus he implies a close relationship between epilepsy, whether grand mal or psychomotor, and some of the now variously diagnosed functional disorders with episodic manifestations such as those mentioned above. It seems to us there is accumulating more and more evidence that paroxysmal activity within the rhinencephalon could very well lead to severely disordered behavior with the adaptive failure so great that such patients are generally considered psychotic. The fact that such behavior showed dynamic content similar to that of dreams (11) and was often more amenable to psychotherapy than pharmacologic treatment has tended to separate this group of disorders from the classic temporal automatism as well as the more complex psychomotor seizures.

The next question one would ask might be as follows: is there evidence from neurophysiologic studies that d-LSD-25 or mescaline does affect the rhinencephalic structures? Although animal studies suggest several subcortical sites of action, a recent study by Killam *et al.* (26) showed that after 50 to 100 μg. of d-LSD-25 there was little effect on the diffuse thalamo-cortical or the reticular activating system. However, he does report a progressive increase in the duration of rhinencephalic seizures produced by stimulation of the pre-commissural fornix after d-LSD-25. This seems to add some weight to the present thesis that at least in the case of d-LSD-25 paroxysmal activity could be induced in rhinencephalic structures.

Inasmuch as our findings, as well as those of others (43), indicate that chlorpromazine is particularly effective in blocking the d-LSD effect, we might ask the question: is there evidence that chlorpromazine acts on the rhin-

encephalic system ? It was found also by Killam (25) that in cats the thalamic recovery time, though markedly depressed by barbiturates, was unaltered by chlorpromazine. However, with chlorpromazine the arousal patterns within the limbic system were markedly depressed. Thus, the effect of chlorpromazine in blocking the action of d-LSD-25 might be due to this depression of the rhinencephalon, which apparently is, at least electrophysiogically speaking, activated by the action of d-LSD-25.

The above discussion could be criticized on the basis that complex behavioral manifestations should not be ascribed to localized anatomical areas without taking into consideration the inter-relationships between the anatomically diffuse physiologic systems, such as centrencephalic, specific afferent, etc., as well as the rhinencephalic. However, thus far the data from our laboratories reported elsewhere (11, 12, 17, 19, 20, 28, 34, 35) demonstrate that dramatic behavioral changes are usually correlated with electrographic changes in the septal and hippocampal-amygdaloid area rather than the other subcortical areas studied. In a careful study of behavior we must consider the introspective aspects which limit our study to humans. At the same time human studies must be therapeutically oriented, hence variables are often difficult to control experimentally. Many of the more precise neurophysiologic techniques are still inapplicable to human investigation. Because of this, generalizations regarding mind-brain relationship must be made cautiously as guides to further research; but is seems to us that paroxysmal activity, at least in the hippocampal, amygdaloid, and septal areas, is correlated with intense emotions, impulsive acting out, depersonalizations, and at times both perceptual and conceptual distortions which descriptively are considered manifestations of psychotic behavior.

SUMMARY

Six patients with chronically implanted intracranial electrodes were studied under the influence of d-LSD-25, 1-LSD-25, mescaline, and correlations attempted between the electrograms and behavioral observations.

An increase in beta activity and a disappearance of alpha characterized in both cortical and subcortical recordings seemed to be associated with anxiety or its derivatives.

Paroxysmal activity induced in the hippocampal, amygdaloid, and septal regions seemed to be associated with overt expressions of disturbed psychotic behavior.

Spread of such paroxysmal activity until it became generalized in the cortex seemed to interfere with the full expression of the psychotic behavior.

Chlorpromazine not only proved an effective blocking agent as far as the behavior was concerned, but also abolished or minimized the appearance of the low amplitude fast activity as well as the paroxysmal subcortical activity. The possible sites of action of LSD-25, mescaline, and chlorpromazine are discussed with reference to the problems of psychomotor epilepsy, episodic psychotic reactions, and schizophrenia.

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THE ELECTROENCEPHALOGRAM AND MENTAL ACTIVITY

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The chief classes of reported variations in the EEG during mental activity may be briefly summarized as follows:

1. During such tasks as mental arithmetic:
   (*a*) alpha blocking;
   (*b*) selectively attenuated alphoid rhythm from temporal areas (Gastaut 1950);
   (*c*) kappa rhythm (Laugier and Liberson 1937; Kennedy *et al.* 1948);
   (*d*) augmented theta rhythm (Arellano and Schwab 1950; Mundy-Castle 1951; Brazier and Casby 1952);
   (*e*) augmented beta rhythm (Mundy-Castle 1951);
   (*f*) suppressed beta rhythm (*ibid*);
   (*g*) selective blocking of individual alpha components (Walter, in Hill and Parr 1950; Esser and Bickford 1950).
2. During affective changes:
   (*a*) augmented theta rhythm (Hoagland *et al.* 1938; Faure 1950; Walter 1950; Mundy-Castle 1951);
   (*b*) suppressed theta rhythm (pleasure — Walter 1950);
   (*c*) suppressed alpha rhythm (e.g. Lindsley 1951);
   (*d*) increased frontal beta rhythm (Cohn 1946; Shpilberg 1947; Faure 1950);
   (*e*) increased alpha rhythm and decreased beta rhythm (Thiesen 1941).

During somatic changes there have been reports of suppressed beta and alphoid rhythms (''rythmes en arceau'') from precentral regions (Gastaut *et al.* 1952; Gastaut 1952b, 1953), whilst visual perception, mental imagery and attention are associated with varying degrees of alpha blocking, sometimes together with either suppressed or augmented beta rhythm, and/or with augmented theta rhythm (Mundy-Castle 1951).

This brief appraisal suggests great variety in possible changes of EEG pattern during mental activity, and that there may be several possible functions associated with the various classes of rhythm. The major problem is to sort out these changes and ultimately classify them in terms of (1) nature of change, (2) nature of stimuli causing change, (3) frequency, amplitude and location (stationary or shifting) of the rhythm or rhythms involved, (4) relationships with other electrical activities, (5) duration of change. One approach which has assisted in the study of these problems is the use of rhythmic photic stimulation (flicker), since electrical rhythms in the brain can often be augmented by appropriate stimulation, thus facilitating their observation (cf. Walter and Walter 1949 a and b; Mundy-Castle 1953 a and b).

The main object of the present study is the elucidation of the nature of electrical changes during mental activity, together with an attempt at a preliminary classification.

METHOD

Three groups were studied as follows:

1. Seventy-two European adults (mostly University students) with a mean age of 23 years, standard deviation 7, were given EEG examinations for a variety of experimental reasons. These recordings also involved eye opening and eye closure in all subjects, mental arithmetic in 64, and visual, auditory and kinesthetic imagery in 59 subjects. Automatic frequency analysis was utilized in all recordings.

2. Sixty-six normal African adults with mean age of 35 years, standard deviation 12. Whilst the primary object of this study was racial comparison (see Mundy-Castle *et al.* 1953), observation was made of the effects of eye opening and eye closure in all cases, and of simple arithmetical problems in 59. A frequency analysis was again always used.

3. To assist in the assessment of the significance of theta rhythm in relation to affective disturbances, 304 routine clinical EEG's were separated into those from subjects in whose case history there had been some comment on bad temper, emotional disturbance or behaviour problem relating to emotional instability, and those without such associated comment. The former will be referred to in subsequent tables under the collective heading of "Bad temper, etc.", the latter as "No bad temper, etc.". The age range of these groups was 3 - 60 years, and patients with organic disease or suspected organic disease were excluded. The two groups, consisting of 137 in the first and 167 in the second, were then compared as regards the occurrence and nature of theta rhythm in their EEG's.

Technical Details.

With the European group, arithmetical problems were multiplicational, e.g. "13 x 19" or "15 x 18" and so on. The instructions for mental imagery were as follows:

1. *Visual Imagery.* "I want you to obtain a visual picture in your mind of (e.g.) so-and-so's face. Tell me when it is clear, and try to keep it until I tell you to let it go."

2. *Auditory Imagery.* "I want you to imagine what it would sound like if (e.g.) rain were beating heavily against the window. Tell me when you can hear it. Try to keep this sound in your mind until I tell you to let it go."

3. *Kinesthetic Imagery.* "I want you to imagine what it would feel like if (e.g.) you were holding both your legs up in the air — do not move them — just try to imagine what it would feel like. Try to keep that feeling until I tell you to let it go."

In all instances, the subject was subsequently interrogated as to the clarity and persistance of his image, and whether other image modes than the one in question were also present.

Appropriate signal marks were made on the record by a switch connected with the time marker pen. Abbreviations of verbal instructions and replies were written directly on the EEG paper at the appropriate times. To facilitate appraisal of changes in the frequency spectrum during these operations, care was taken to ensure as far as possible that all instructions were completed at the end of an analyzer epoch, so that changes in subjective state would coincide with a new epoch. At least one complete epoch was allowed to elapse before requesting the subject to dismiss his mental image.

With the African subjects, mental arithmetical problems were far easier than with the European group, ranging from e.g. 2 + 3 to, e.g., 24 + 19.

Affective Changes.

No controlled study was made of changes in emotional level. Nevertheless, affective variations were not uncommon, either as an accompaniment to the tasks already mentioned or during flicker, or merely by some chance incident during recording, particularly if this involved demonstration to other persons, as it often did with the student group. Isolated experiments were also made of the effects of pleasurable stimulation, in the form of gentle caressing of the face, neck or other parts of the body. Occasional samples of EEG changes during affective changes among the clinical group were also fortuitously available, particularly in the younger age-groups.

Flicker.

As already mentioned, flicker can be helpful in the study of EEG changes during altered state, since specific rhythms can be evoked or enhanced by appropriate stimulation. The majority of subjects involved in the present investigations were also subjected to full-scale flicker testing. In many instances, observation was also made of the effects of eye opening, eye closure and mental activity during flicker at various frequencies.

RESULTS

Eye opening, Mental Arithmetic and Imagery, Normal European Group.

In these categories the following EEG changes were observed:

Beta Rhythm: augmentation; suppression.

Theta Rhythm: augmentation; suppression (rare).

Alpha Rhythm: varying degrees of blocking, classified on the scale 0 - 1 - 2 - 3, where 0 = no change, 3 fully blocked.

A slight increase in alpha frequency was occasionally noted during mental arithmetic, and usually on eye closure.

Statistical analysis revealed that a number of percentages of these EEG changes according to the mental and visual operations were significantly different, as follows:

Augmented Beta Rhythm: greater during visual imagery and mental arithmetic than during eye opening.

Suppressed Beta Rhythm: greater during eye opening than during kinesthetic imagery.

Augmented Theta Rhythm: none significant.

Suppressed Theta Rhythm: none significant.

Alpha Blocked 0: greater during auditory and kinesthetic imagery than during eye opening, visual imagery and mental arithmetic; greater during kinesthetic than during auditory imagery.

Alpha Blocked 1: greater during auditory imagery and mental arithmetic than during eye opening; greater during kinesthetic than visual imagery.

Alpha Blocked 2: greater during mental arithmetic than during kinesthetic imagery.

Alpha Blocked 3: greater during eye opening than during visual, auditory and kinesthetic imagery and mental arithmetic; greater during visual imagery and mental arithmetic than during auditory and kinesthetic imagery.

An overall appraisal of the distribution of these EEG changes according to mode of altered experience is shown in figure I, where the relative percentages are displayed as a bar diagram.

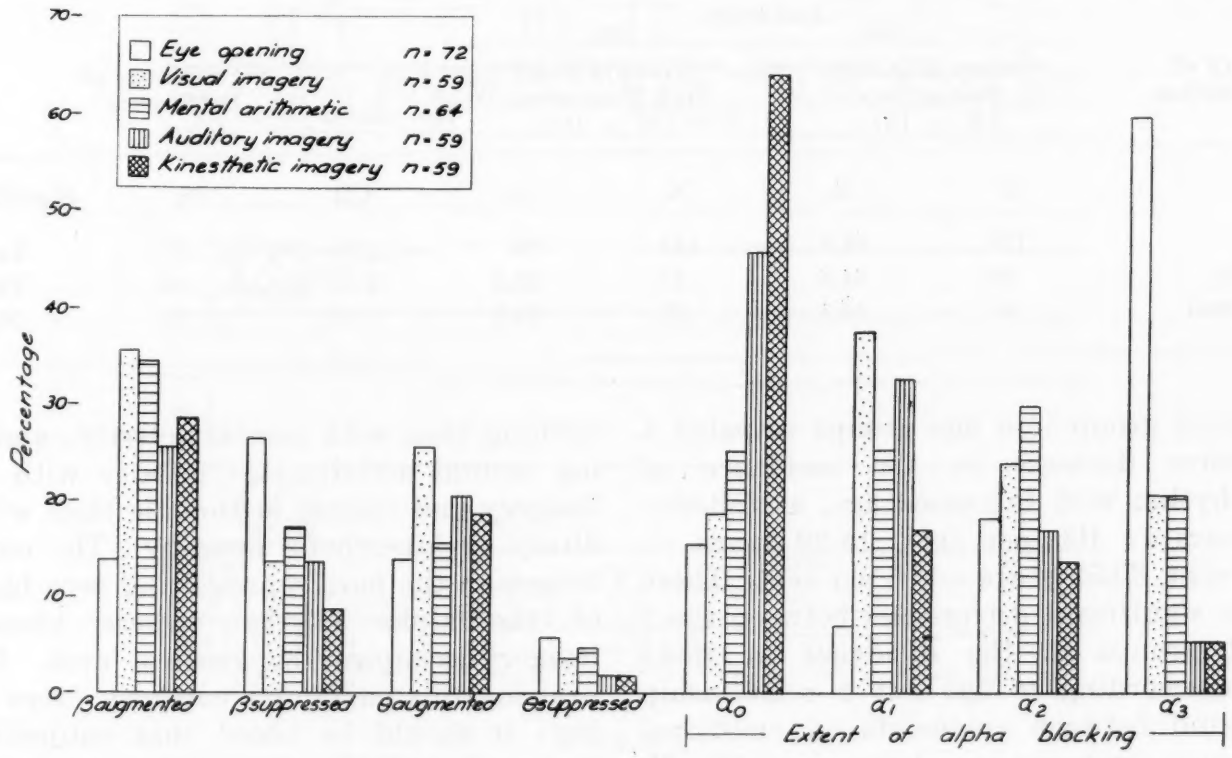

Fig. 1.

Racial Differences.

The figures for eye opening and mental arithmetic were compared with the corresponding figures from the African group. There are only two significant differences, both during eye opening, where theta augmentation and alpha blocking 1 occurred more often among the Africans. The probabilities were at the 5 per cent and 2.5 per cent level respectively.

Theta Rhythm and Temper, Clinical Group.

The incidence, percentage and significance of difference in 3 categories of theta rhythm (any, excessive, paroxysmal) in the two clinical groups were examined. There are two significant differences: the group in which some disturbances relating to emotionality had been noted showed (1) a significantly greater incidence of theta rhythm, and (2) of "excessive" theta rhythm, than the control group (see table I). Also, subdivision of the overall clinical group into age groups revealed a progressive decrease in the incidence of theta rhythm with increased age, as follows: 3-14 years = 100 per cent, 15-29 years = 83 per cent, 30-59 years = 70 per cent. There were no significant differences between the 2 clinical groups in the incidence of theta rhythm according to age but a relationship was found between comments on emotional disturbance and age, as shown in table II, which implies that in these groups youth is associated with a greater incidence of emotional instability than is older age.

Qualitative Observations.

The following figures demonstrate the types of EEG change under consideration. Changes associated with mental arithmetic and mental imagery are shown in figures 2 to 5, while in figures 6A to 8 the use of flicker for the study of EEG changes is demonstrated. Although changes during affective variation emphasized theta rhythm, it should not be forgotten that suppressed alpha rhythm and increased beta rhythm are often associated with hyperemotional states.

TABLE I

THETA RHYTHM AND TEMPER
CLINICAL GROUPS

Category of Theta Rhythm	Incidence				Significance of Difference		
	Group with Bad Temper etc. (N = 137)		Group without Bad Temper etc. (N = 167)				
	N	%	N	%	CR	P	Significant
Any	130	94.9	142	85	2.95	< .001	Yes
Excessive	84	64.6	74	52.1	2.12	< .05	Yes
Paroxysmal	47	36.1	65	45.8	1.62	> .10	No

DISCUSSION

Alpha Rhythm. The results of the statistical analysis confirm the view originally expressed by Adrian and Matthews (1934) that the alpha rhythm is very much concerned with visual processes. This may be observed clearly in figure 1, which shows that maximal blocking of the alpha rhythm is far greater with eye opening than with mental activity; and, during mental activity, far greater with visual imagery and mental arithmetic than with auditory or kinesthetic imagery. The converse is seen in the bars representing zero blocking of the alpha rhythm, where kinesthetic imagery occupies the greatest area. In appraising this particular category (zero blocking) it should be noted that subjects with "minus" ("M") type alpha rhythms have not been excluded, hence the superficially surprisingly high incidence of zero-blocks with

TABLE II

CONTINGENCY TABLE: ASSOCIATION BETWEEN AGE AND REFERENCE TO BAD TEMPER ETC.

Age in years:	3-14	15-29	30-59	Totals
Bad Temper etc.	89	29	19	137
No Bad Temper etc.	71	58	38	167
Totals	160	87	57	304

$\chi^2 = 14.12$, df = 2, $p < .001$

eye opening; but the fact that "M" type alpha rhythms are associated with predominantly visual imagery is further support for the view that the alpha rhythm is closely associated with visual systems in the brain (Golla, Hutton and Walter 1943; Short 1953; R. Walter and Yeager 1956; Barratt 1956).

There is no doubt, however, that the alpha rhythm may be fully blocked without any conscious involvement of visual activities, and most of the evidence suggests that this is attributable to an attention or alerting factor, as also originally invoked by Adrian and Matthews as a requisite of alpha blocking. But the present study also reveals that concentrated attention can occur without any blocking of the alpha rhythm, as indeed can a visual image which is assessed as of maximal

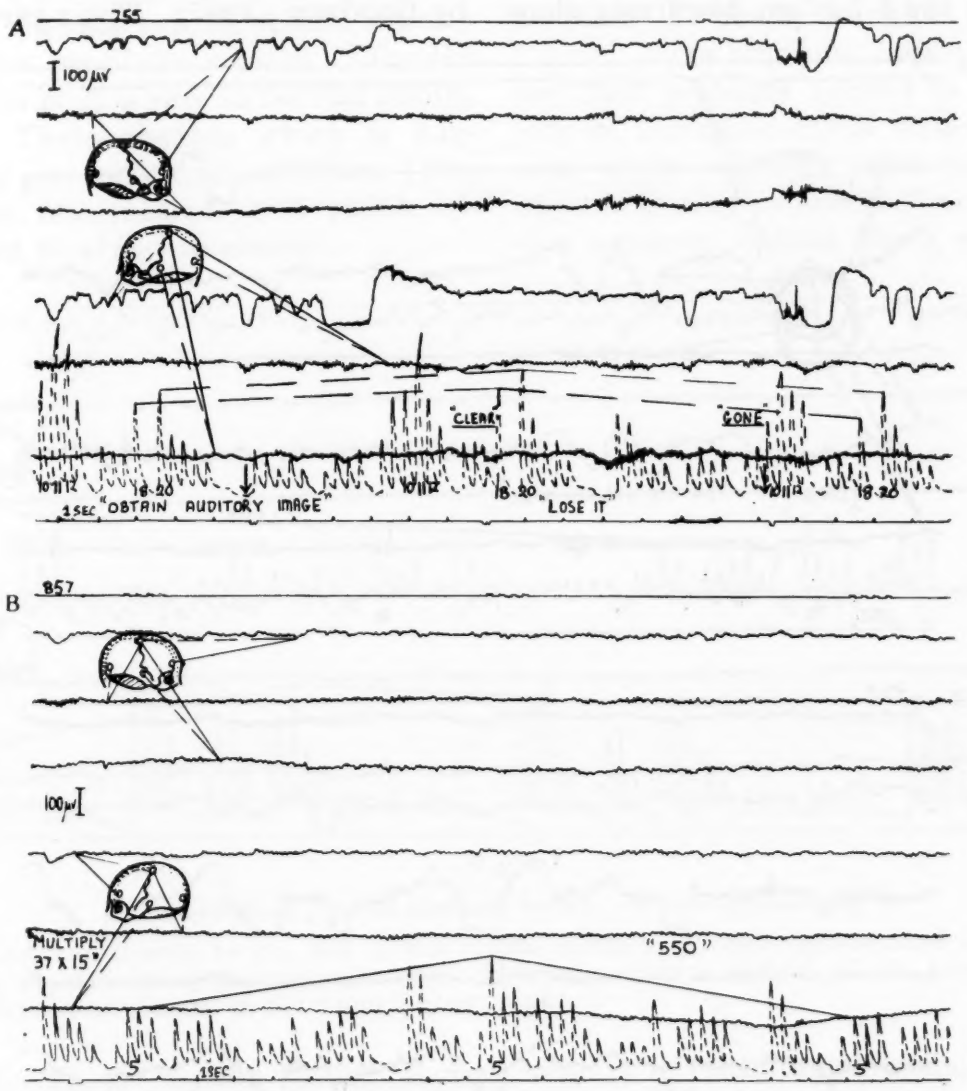

Fig. 2

A. *Augmented beta rhythm: Auditory imagery.*

Normal female, 20 yr. Analyzer derivation (AN) = right parieto-occipital: 18-20 c/sec. activity increased during an auditory image (rain beating against window). Note complex changes in α frequency spectra and relative lack of α blocking.

B. *Augmented theta rhythm: Mental arithmetic.*

Normal female, 21 yr. AN = left fronto-parietal: marked increase in 5 c/sec. rhythm during solution of arithmetical problem. Note also increased 6-11 c/sec. activity as shown by analyzer.

clarity. These facts should be accounted for in any adequate theory concerning the generation or function of the alpha rhythm.[1]

Theta Rhythm.

Mundy-Castle (1951) reported that rhythms within the 4-7 c/sec. band may show variation during visual and/or mental tasks, or during slight changes in temper. He distinguished two classes of theta rhythms, those which are harmonically related to alpha frequencies and those which are not. The former have been called "slow alpha variants" by Goodwin (1947). Their rarity among normal adults is confirmed in the present study, since there were only 15 (11 per cent) in the combined normal groups, and most of these were but fleetingly apparent; only 3 (2 per cent) were present sufficiently often to observe suppression during eye opening. The

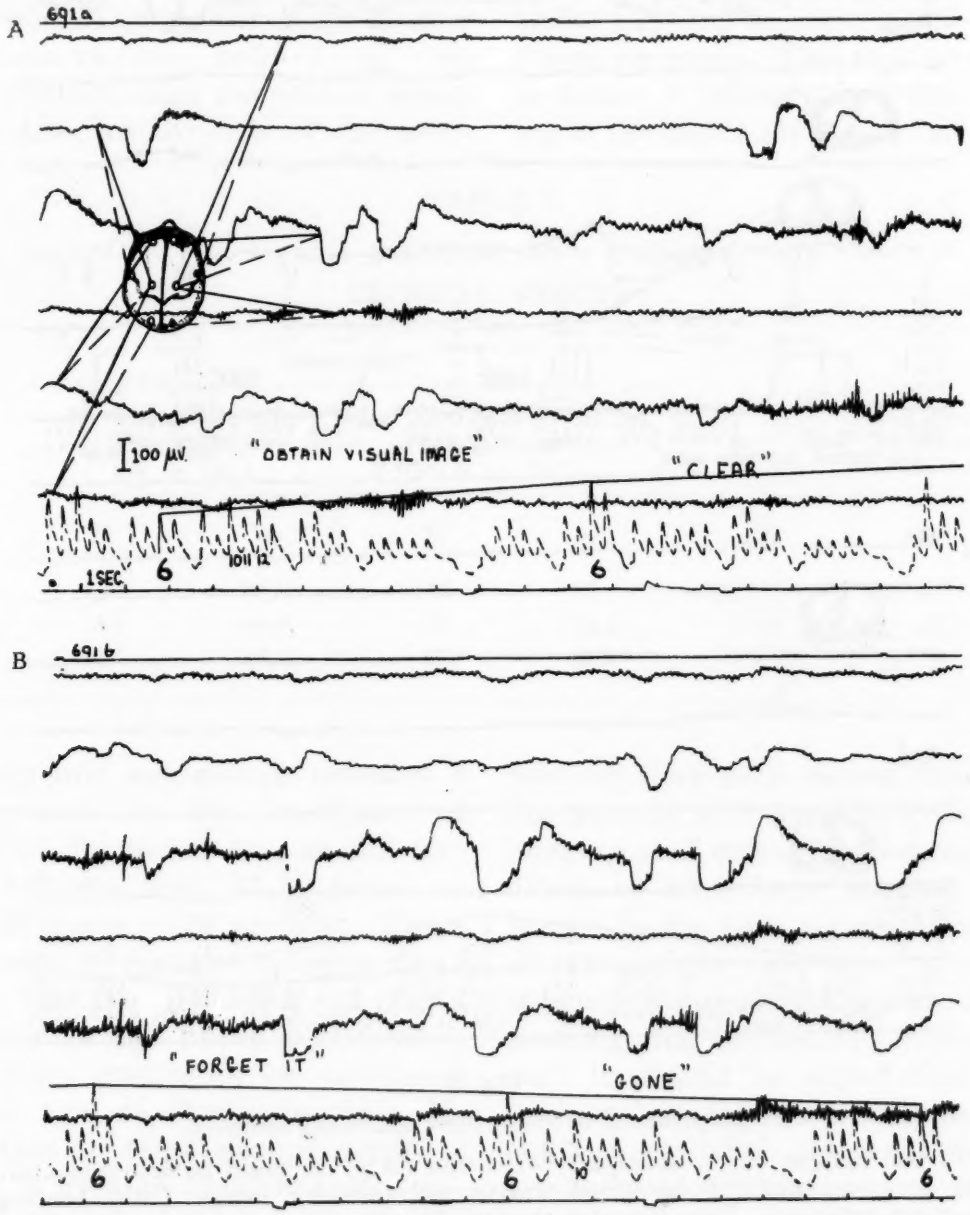

Fig. 3 A and B

Augmented theta rhythm: Visual imagery.

Normal female, 26 yr. AN = right parieto-temporal: clear increase in 6 c/sec. rhythm (generalized, strongest anteriorly) during presence of visual image. α blocking also clear.

[1] Incidentally, the paper of Drever (1955) has just come to the author's attention. In this work, he tested the hypothesis that disappearance of alpha rhythm during mental work is associated with visual imagery; his results suggest that this is not necessarily true, and that the hypothesis appears to be an oversimplification and in need of some reformulation. This conclusion accords with that presented above.

present data suggests that 4-7 c/sec. rhythms which are not alpha variants should be further differentiated into at least three groups, which, for the purposes of the present discussion, will be labelled as follows:

Theta I. Theta rhythm which is suppressed by eye opening and/or mental activity yet which is not an alpha variant. Like the slow alpha variant, it is rare in normal adults.

Theta II. Theta rhythm which is augmented during non-emotional activities (perceptual and/or imaginative) and which appears unrelated to affective change.

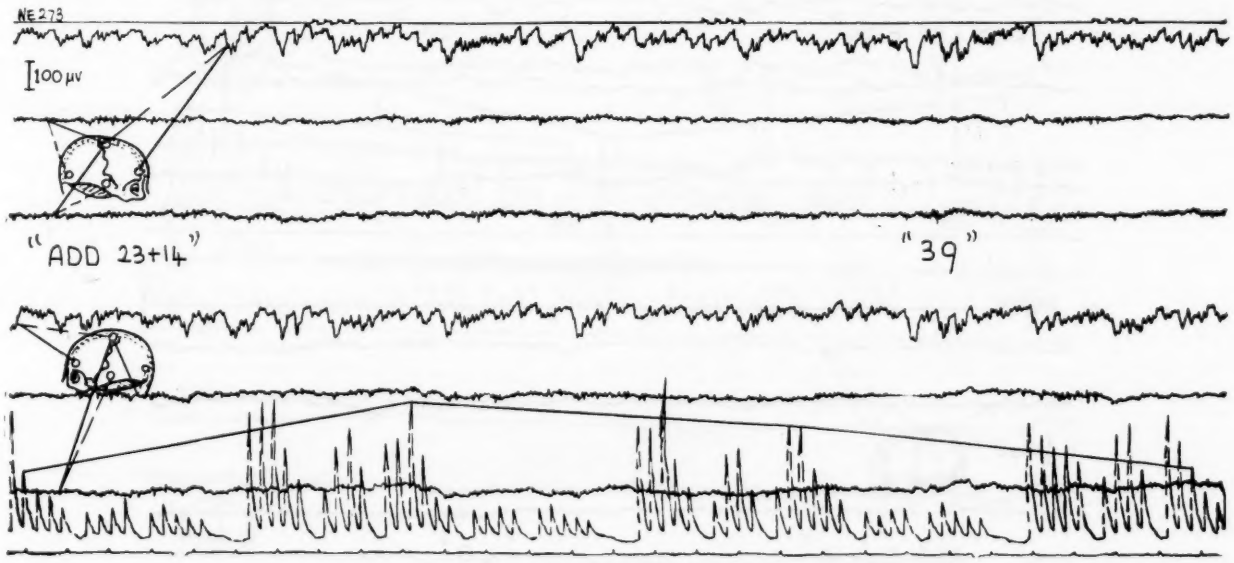

Fig. 4

Augmented frontal alphoid rhythm: Mental arithmetic.

Normal African female, 33 yr. AN = left fronto-parietal: marked augmentation of a frontal 10 c/sec. rhythm during mental arithmetic. This is possibly a variant of the kappa rhythm. Note independent changes in the 8 and 9 c/sec. peaks.

Theta III. Theta rhythm which shows variation during emotional activities.

On this classification, the tentative suggestion that augmented theta rhythm during imagination might be related to slight changes in temper would relate only to theta III. Inclusion of the second class (theta II) is necessary since in the present study there were several instances of augmented theta rhythm during purely intellectual (non-emotional) activity, and in which the subject denied explicitly any conscious experience of altered temper. Rather does it seem that theta II falls into the same category as the kappa and other rhythms reported as prominent during mental activity. Further study of theta II must be concerned primarily with topography: there is little doubt of its occurrence. It should also be noted that there are no significant differences in the incidence of suppression or augmentation of theta rhythm among eye opening, mental arithmetic and the three forms of imagery.

The group of 4-7 c/sec. rhythms labelled as theta III comprises what might be called "true" theta rhythms, in the sense that they are most probably related to functional activity in thalamo-cortical structures. The present study confirms that augmented theta rhythm during intellectual activity *may* be of this category, whilst there were several instances of variations in theta rhythm associated with rather more profound disturbances of emotional state.

The consistent trend in the history of EEG relating theta rhythm with emotional lability and cortical immaturity is maintained by the present results concerning significant associations between age, reports of emotional instability and the incidence of theta rhythm. Similar indications have been given by Hill (1952), although not all were backed by statistical significance. It does, however, seem that these three variables are interrelated, and that carefully controlled EEG studies may clarify this sphere of personality assessment. Such research will also establish whether the three groups of theta rhythm which have been

differentiated in the present study are in any way related to one another. In this connection it should be recalled that Hill (1952) classifies the slow alpha variant as an EEG maturation defect.

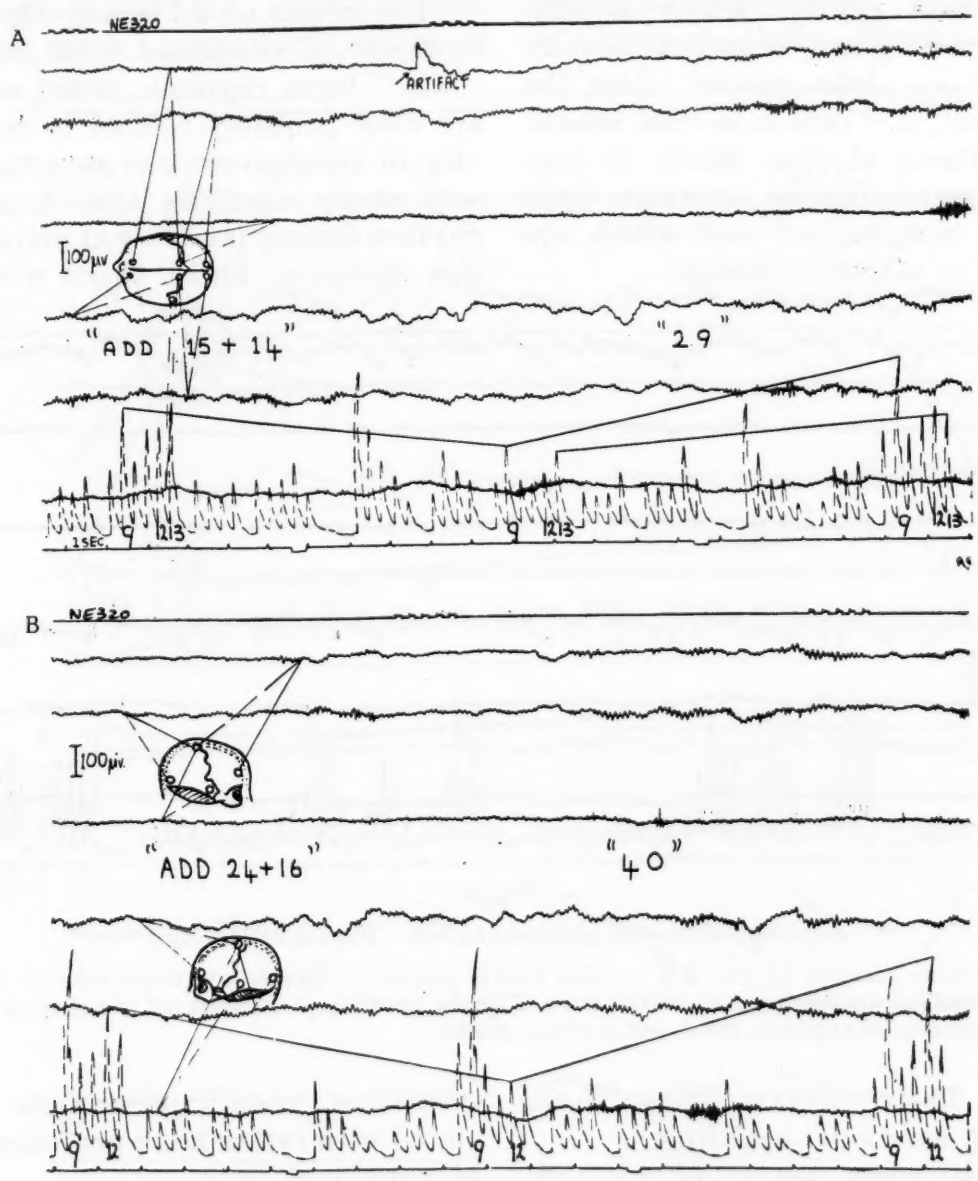

Fig. 5

Selective blocking of frontal alphoid rhythm: Mental arithmetic.

Normal African male, 26 yr. (A) AN = left fronto-parietal: 9 c/sec. rhythm markedly decreased during mental arithmetic. Rhythms at 11-13 c/sec. are also blocked. (B) AN = left parieto-occipital: the 9 c/sec. rhythm is unaffected by mental arithmetic, whilst the 11-13 c/sec. components are very much attenuated. These two samples suggest that the 9 c/sec. activity is being selectively blocked in the frontal regions during mental arithmetic.

Beta Rhythm.

Mundy-Castle (1951, 1953b) has suggested that, in terms of responsiveness, there are two broad groups of beta rhythm, one showing suppression during cortical activity and often, though not invariably, harmonically related to alpha frequency, the other being augmented during cortical activity. As with theta rhythm, the two subgroups in the first class might be called beta I and "fast alpha variant" (after Goodwin 1947) depending on their relationship with the alpha rhythm, whilst the second group might be called beta II.

Mundy-Castle (1951) proposed that the former may possess a function similar to one of those of the alpha rhythms, namely that it

may be a component incorporated in sensory analyzing systems; and that the latter (beta II) represents an accelerated process resultant on scansion of the projection and/or association areas in which there is neuronal activity could be made according to location, since, as will be discussed in a moment, both the more anterior and the occipital beta rhythms could relate to similar mechanisms yet deal with different media.

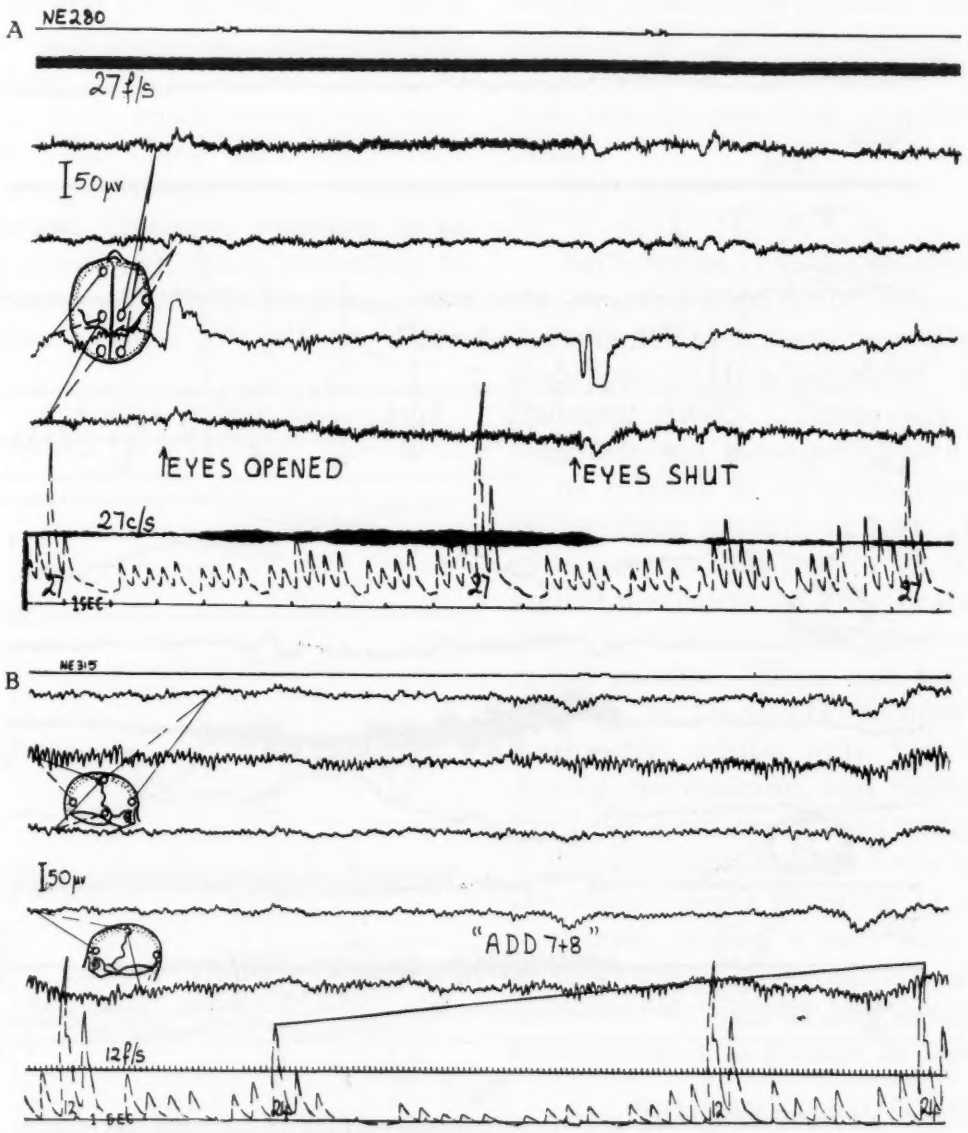

Fig. 6

A. *Flicker responses in beta range augmented by eye opening.*
Normal African male, approx. 22 yr. Flicker at 27 f/sec. AN = right parieto-occipital: eye opening causes marked augmentation of responses at 27 c/sec. Such augmentation is common in the 25-35 f/sec. range.

B. *Flicker responses in beta range augmented during mental arithmetic.*
Normal African male, approximately 22 yr. Flicker at 12 f/sec. AN = left parieto-occipital: marked augmentation of 2nd harmonic (24 c/sec.) during mental arithmetic. Note unchanged fundamental 12 c/sec. response.

consequent on the presentation of either internally or externally derived perceptual patterns. Beta II would then reflect a part of the process of mediation of information within the brain. Further classification of this group

The statistical data concerning beta rhythm and those presented in figure 1 support this bifold classification of beta rhythm according to suppression or augmentation during cortical activity. Blocking of beta rhythm occurs

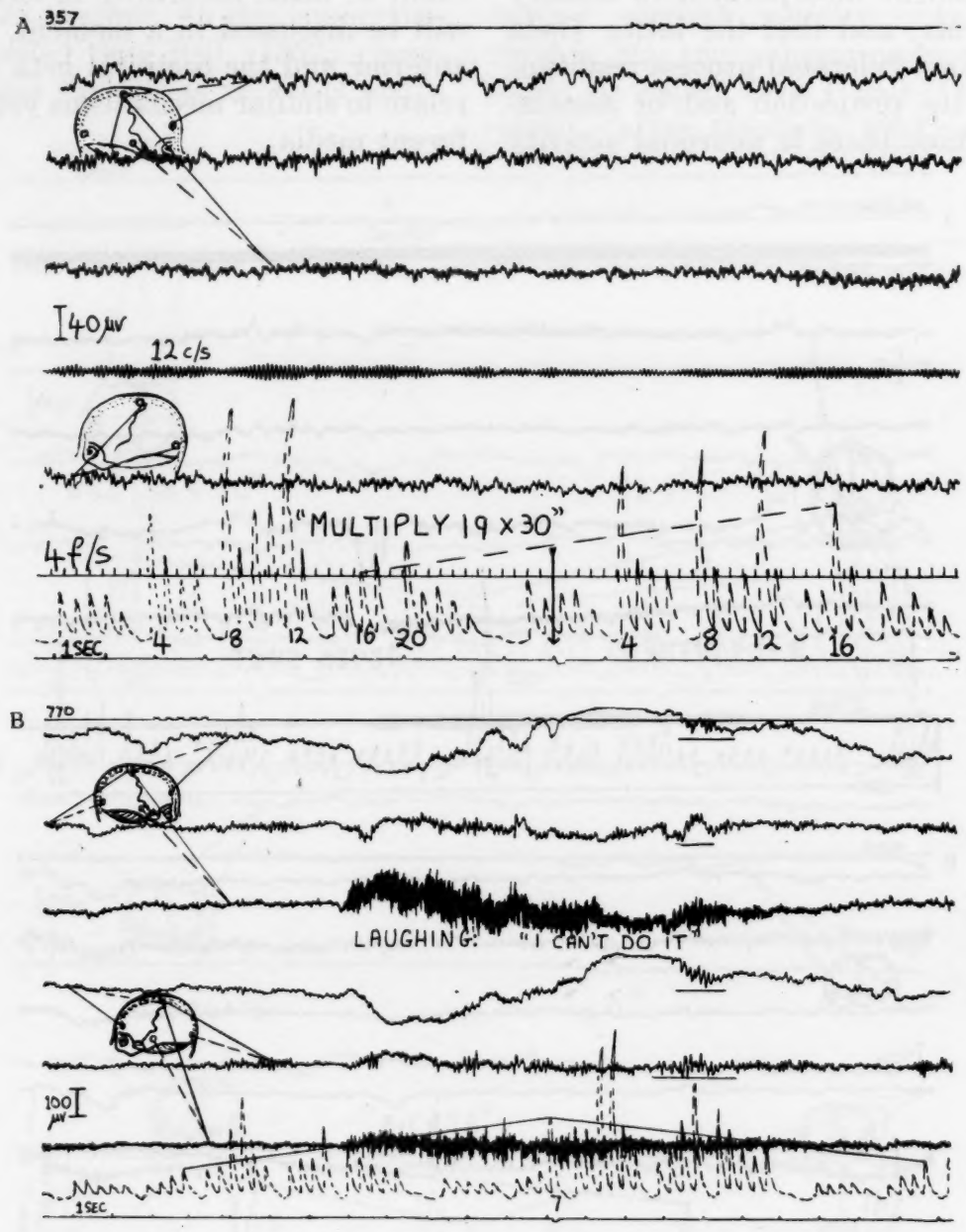

Fig. 7

A. *Differential changes in components of flicker response during mental arithmetic.*

Normal female, 21 yr. Flicker at 4 f/sec. AN = left parieto-occipital. The 1st and 4th (16 c/sec.) harmonics are augmented during mental arithmetic, whilst the 2nd (8 c/sec.) and 3rd (12 c/sec.) are suppressed. Thus components with theta and beta frequencies have been augmented, those with alpha frequencies suppressed.

B. *Theta rhythm augmented during embarrassment.*

Normal female, 20 yr. AN = left parieto-occipital. She had been given an arithmetical problem, but was unable to do it, despite its relative simplicity. She became flustered and embarrassed and laughed nervously. During this period there occurred a short generalized burst of high voltage theta rhythm. Comparable bursts did not occur in the resting EEG. Traces of theta rhythm can also be detected in the 6 sec. prior to the burst whilst both α and β amplitudes are increased, although the latter may be contaminated by EMG activity.

more often during eye opening than in any other category. Eye opening involves projection of sensory patterns on the visual cortex, and these must be analyzed and transformed into suitable (? temporal) patterns for transmission to other areas. The blocking of the alpha rhythm and the associative blocking of certain (especially posterior) beta rhythms suggests that these may be related to alpha function and as such much concerned with visual activities. The fact that kinesthetic imagery shows a significantly lower incidence of beta suppression than eye opening is in support of this argument, since according to the figures relating to alpha blocking, this task is the least visual of all in these experiments.

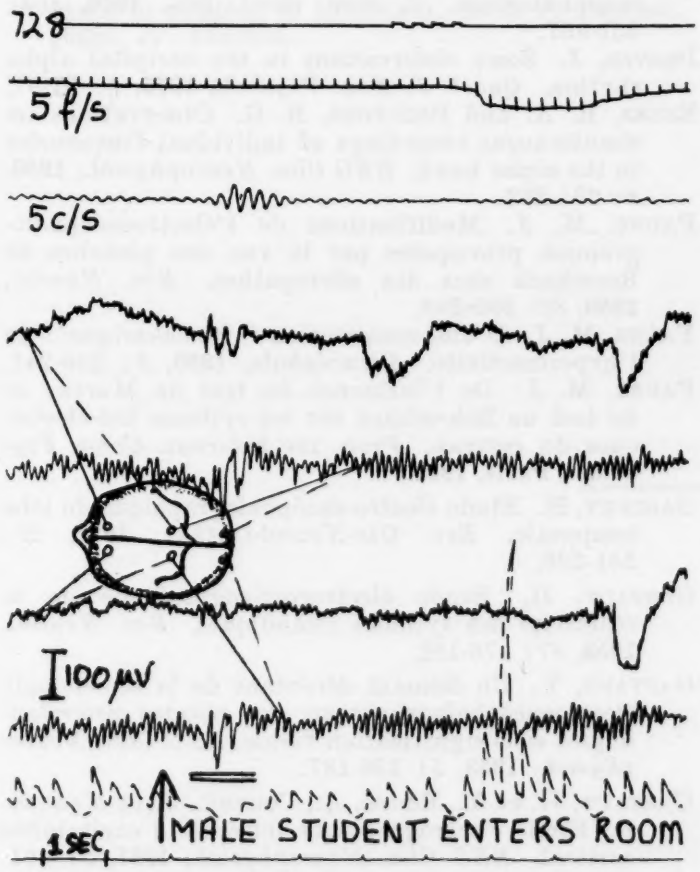

Fig. 8

Theta rhythm augmented during emotional excitement.

Normal female, 17 yr. Flicker at 5 f/sec. There were several female friends (all University students) in the room and there was a knock at the door. Subject did not wish anyone else to enter, but despite her protestations the door was opened and a male student entered, causing much laughter from the watching female students. At this moment there was a generalized burst of 5 c/sec. activity in the EEG. Subject afterwards stated that she was "emotionally excited" at this point.

It would be interesting to know whether the blocking behaviour of precentral beta rhythms and the alphoid *rythme en arceau* is in any way related to the registration of changes in body posture and limb position, or to reference to existing posture; such a possibility recalls the postural schema theory of Head (1920) and its elaboration by Bartlett (1932) to include all individual experience, and has far-reaching psychological implications.

Racial Differences.

Differences in the main characteristics between the EEG's of normal Europeans and normal Africans have been discussed in detail elsewhere (Mundy-Castle, McKiever and Prinsloo 1953). There are no gross differences, and those which are present appear to be related to environmental and cultural rather than genetic factors. The present results suggest that insofar as the electrophysiological mechanisms of the brain are concerned, there is also little difference between these racial groups. There are no significant differences in the EEG changes during mental arithmetic, whilst only two are significant during eye opening, and neither of these is at the 1 per cent level: one (theta augmentation) is just significant at the 5 per cent level, whilst the other (alpha blocking 1) is at the 2.5 per cent level, neither a very convincing criterion in this type of investigation, and certainly insufficient to suggest any great distinction between these two groups in this respect.

SUMMARY AND CONCLUSION

1. An analysis is made of changes in the EEGs of African and European normal adults during eye opening and mental arithmetic, and for Europeans only during visual, auditory and kinesthetic imagery. These studies were made both with and without simultaneous photic stimulation. Data are also presented concerning theta rhythm, emotion and emotional instability, derived from the EEGs of 304 clinical cases differentiated according to whether or not emotional disturbance was a feature of their case histories.

2. The results concerning alpha rhythm support the view that it is related both to

visual processes and to an attention or alerting factor. It is important, however, that attention, such as concentration during mental arithmetic or mental imagery, can occur without alpha blocking, as also can *visual* imagery reported as of maximal clarity. There is thus no one-to-one relationship between alpha blocking and either visualization or attention.

3. Rhythms at alpha frequency from frontal and temporal areas are distinguished from alpha rhythms as "alphoid". They may behave independently of the alpha rhythms during mental activity, showing either no change, or being augmented or suppressed.

4. A fourfold classification of 4-7 c/sec. rhythms is suggested as follows:

(i) slow alpha variants (rare in normals);

(ii) "theta I": not harmonically related to the alpha rhythm, yet suppressed by eye opening and/or mental activity;

(iii) "theta II": augmented during perceptual and imaginative activities and apparently unrelated to affective changes. Possibly similar to kappa and related rhythms;

(iv) "theta III": varies during emotional activities. Results from the analysis of theta rhythm in the clinical group maintain the consistent historical trend associating theta rhythm with emotional and cortical immaturity.

5. A bifold classification of beta rhythm is suggested as follows:

(i) "beta I": including fast alpha variants, and comprising fast rhythms which are suppressed during cortical activity;

(ii) "beta II": fast rhythms augmented during cortical activity.

It is tentatively proposed that the first relate to the analysis and registration of data projected on the cortex, the second to the mediation of information within the brain.

6. The study confirms that photic stimulation can assist in the analysis of changes in the EEG during perceptual or mental activity, by selectively augmenting specific rhythms so that their behaviour can more readily be observed.

7. No important differences were found between normal Africans and normal Europeans in respect of EEG changes during eye opening or mental arithmetic.

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ANNOUNCEMENTS OF MEETINGS

EASTERN ASSOCIATION OF ELECTROENCEPHALOGRAPHERS

Annual Meeting:

December 11, 1957

Blumenthal Auditorium,

Mount Sinai Hospital, New York City.

Laurentian Meeting:

St. Adele Lodge, St. Adele, P.Q.

February 28-March 2, 1958

Symposium: The Electroencephalogram in Endocrine Disorders,

Dr. Gilbert Glaser, Chairman.

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

The Annual Meeting of the Association for Research in Nervous and Mental Disease will be held on December 13 and 14, 1957 at the Hotel Roosevelt, New York City. The subject of the meeting will be "The Effect of Pharmacologic Agents on the Nervous System".

THE AMERICAN PSYCHOSOMATIC SOCIETY

FIFTEENTH ANNUAL MEETING

The American Psychosomatic Society will hold its Fifteenth Annual Meeting at the Netherland Hilton in Cincinnati, on Saturday and Sunday, March 29 and 30, 1958.

The program Committee would like to receive titles and abstracts of papers for consideration for the program, no later than November 15, 1957. The time allotted for presentation of each paper will be twenty minutes.

Abstracts of the papers in octuplicate, should be submitted for the program committee's consideration, to the Chairman, at 551 Madison Avenue, New York 22, New York.

EEG FREQUENCY-PATTERN VARIATION AND INTELLIGENCE
A Correlational Study

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Attempts to demonstrate a relationship between brain wave activity and intelligence have generally yielded negative results (Lindsley 1944; Ellingson 1956). In his book, *The Living Brain,* Walter (1953) reports observations which suggest a possible positive relationship between EEG frequency-pattern variation and intelligence. In data from his automatic frequency analyser, Walter observed a greater variation of the frequency "spectrum" among his "more brilliant colleagues" than among his "duller patients". Patterns derived from 10-sec. epochs varied more from the average spectrum for 60 sec. among the former than among the latter. He suggested the term *versatility* to describe the tendency toward greater pattern variability. This may be related to Walter's concept of brain rhythms as scanning mechanisms, brains with more numerous and variable scanning rhythms being more versatile.

The present paper reports an attempt to determine if a correlation might exist between an objective measure of intelligence and EEG frequency-pattern variation, using a different method of measuring the latter from that used by Walter. The hypothesis to be tested is that there is a positive relationship between intelligence and EEG frequency-pattern variation. To support this hypothesis the data must show a significant tendency for high variation of frequency pattern to be associated with high intelligence and low variation (or regularity) of pattern to be associated with lower intelligence.

MATERIALS AND METHOD

The subjects were 26 "normal" psychiatric aides, 15 males and 11 females, and one high-grade mentally deficient young man, hospitalized for observation, who was considered neither mentally ill nor brain damaged. The age range was 19 to 40 years, mean 26.4, standard deviation 5.8. Thirteen of the aides were full-time, permanent employees whose education ranged from grammar school to two years of college. Thirteen were part-time or summer employees enrolled as undergraduate, graduate, or medical students in this and neighboring universities. All subjects had normal EEGs.

The subjects were given a short form of the Wechsler-Bellevue Intelligence Scale, Form I, consisting of the Comprehension, Arithmetic, Block Design, and Digit Symbol subtests. The weighted subtest scores were extrapolated to yield an estimate of the full-scale IQ. This quartet of subtests has been shown by McNemar (1950) to correlate highly with full-scale IQ ($r = .932$), and to be the most valid of the possible 4-subtest combinations.

The subjects' EEGs were recorded with an Offner Model D-4 electroencephalograph. Concurrent frequency analysis was performed by means of an Offner Frequency Analyser (fig. 1). The alignment of the analyser was checked before running each subject. Ten artifact-free 10-sec. epochs were recorded from each of the following electrode pairs, left occipital-left ear (LO-E), left precentral-left ear (LpC-E), left occipital-left parietal (LO-P), left occipital-left precentral (LO-pC), and finally LO-E again, to provide data for a test of the reliability of the obtained estimates of frequency-pattern variation.[1] The subject

[1] The repeat procedure was unintentionally omitted in 3 cases so the number of cases for the reliability data is 24.

was given no instructions save to lie still with eyes closed. The procedure was interrupted between runs to insure against the subject becoming drowsy. If a subject did become drowsy, the procedure was repeated and the "drowsy epochs" discarded.

In order to obtain a single summary measure of epoch to epoch agreement among frequency-patterns the coefficient of concordance or Kendall's W (Kendall 1948) was computed. The procedure is as follows. The heights of the 14 "spikes" of the analyser write-out for frequencies 6 to 22, inclusive, were ranked, the tallest spike being given the rank of 1 and the shortest 14.[1] The ranking procedure was repeated for each of the 10 successive epochs of each run (LO-E_1, LO-E_2, LpC-E, LO-P, and LO-pC). The 10 sets of rankings for each run for each subject were tabled, and Kendall's W was then calculated for each table, using the correction for ties. The value of the resulting Ws is dependent on the similarity among the 10 sets of rankings for each electrode pair for each patient. W can vary between 0.0 and 1.0. The higher the value of W the greater the similarity among the sets of ranking, the lower the value of W the less the similarity. In this instance, the higher the W the greater the interepoch similarity of frequency pattern, the lower the W the less the similarity (the greater the variation).

The 27 subjects were then ranked with respect to each of the 6 derived measures: estimated IQ, W(LO-E_1), W(LO-E_2), W(LpC-E), W(LO-P), and W(LO-pC). The reliability of the obtained estimates of frequency-pattern variation (Ws) was tested by calculating the rank correlation (Spearman's ρ) between W(LO-E_1) and W(LO-E_2). As a matter of methodological interest ρs were calculated for the W data derived from the different electrode pairs. Finally ρs were calculated between estimated IQ and Ws for each of the four electrode pairs.

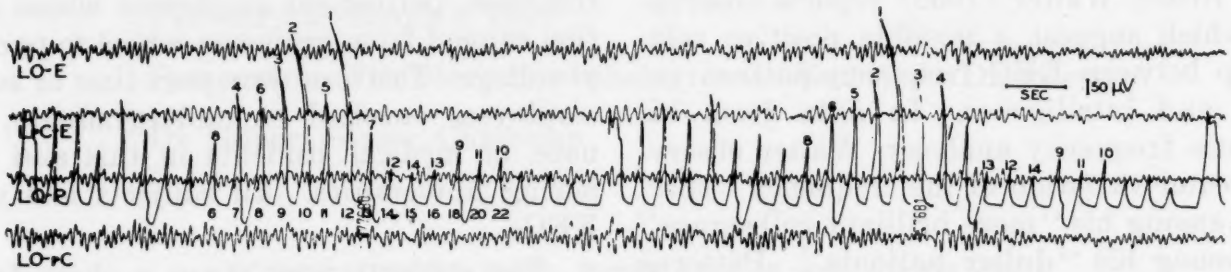

Fig. 1

EEG tracings with superimposed automatic frequency analyser write-out. See text for explanation of the electrode pairs. Two 10-sec. epochs are shown. The top channel is the one analysed. The frequencies used in the present study are indicated by the numbers under the appropriate analyser "spikes" in the epoch on the left. The rankings of "spike" heights in both epochs are shown by the numbers at the tips of the "spikes". The subject is a 21 year old college student, estimated IQ 118.

The specific hypothesis to be tested now can be stated as follows: there is a significant negative correlation (ρ) between estimated IQ on the one hand and W(LO-E), W(LpC-E), W(LO-P), or W(LO-pC) on the other. (The hypothesis was of course tested statistically in the null form.) To support the hypothesis one or more of these four correlations must be significantly negative.

RESULTS

The 27 estimated IQs obtained ranged from 64-147, mean 116.9, standard deviation 18.2.

The 132 Ws obtained ranged from .64 to .99; 82 of them exceeded .90. All Ws are statistically significant (Ps $< .001$), demonstrating the inter-epoch similarity of the EEG frequency-pattern when the subject remains in a constant state.

[1] Spikes less than 16 mm. in height were ranked in a last place tie, since it was found that spikes that high could be obtained in the absence of input from the EEG amplifiers. The delta frequency band (1.5-3.5 c/sec.) was omitted because of its sensitivity to movement artifacts of even low amplitude. Frequencies 4, 5, 24, 27, and 30 were omitted in order to avoid an excessive number of last place ties, since these spikes do not often show significant elevation in normal EEGs with our instruments.

The ρ between W(LO-E_1) and W(LO-E_2) is .87, which is statistically significant ($P < .001$), indicating the reliability of the estimates of frequency-pattern variation (Ws). The correlations between Ws derived from the 4 electrode pairs are given in table I.

TABLE I
RANK CORRELATIONS (ρs) AMONG FREQUENCY-PATTERN VARIATION MEASURES DERIVED FROM SEVERAL BRAIN AREAS FOR 14 FREQUENCIES

Electrode Pairs	Electrode Pairs		
	LpC-E	LO-P	LO-pC
LO-E	.69 **	.73 **	.74 **
LpC-E		.62 **	.48 *
LO-P			.73 **

* statistically significant ($P < .02$)
** statistically significant ($P < .001$)

They indicate that there is a high degree of similarity in frequency-pattern variation measured from different areas of the brain of the same individual, even when not measured at exactly the same time.

The correlations between estimated IQ and Ws for the 4 electrode pairs are given in table II. Since they are negligible and do not

TABLE II
RANK CORRELATIONS (ρs) BETWEEN ESTIMATED IQ AND EEG FREQUENCY-PATTERN VARIATION (Ws) FOR 14 FREQUENCIES

IQ, W(LO-E)	.123
IQ, W(LpC-E)	—.071
IQ, W(LO-P)	.098
IQ, W(LO-pC)	.0004

differ significantly from zero, the null hypothesis cannot be rejected, and the hypothesis being tested is not supported.

Inasmuch as Dr. Walter has informed us (personal communication) that the relationship he observed obtained only for the alpha frequency band, 8-13/sec., we have reanalysed our raw data for those 6 frequencies over 10 epochs.[1] The 132 Ws obtained ranged from .49 to .99; 62 of them exceeded .90; all were statistically significant; and the distribution of Ws was, as in the previous analysis, skewed to the low end. The correlations between Ws derived from the 4 electrode pairs are given in table III. It will be noted that about the

TABLE III
RANK CORRELATIONS (ρs) AMONG FREQUENCY-PATTERN VARIATION MEASURES DERIVED FROM SEVERAL BRAIN AREAS FOR 6 FREQUENCIES

Electrode Pairs	Electrode Pairs		
	LpC-E	LO-P	LO-pC
LO-E	.56 **	.62 ***	.70 ***
LpC-E		.41 *	.50 **
LO-P			.76 ***

* statistically significant ($P < .05$)
** statistically significant ($P < .01$)
*** statistically significant ($P < .001$)

same relationships obtain among electrode pairs as when the analysis is based on 14 frequencies (table I). Correlations between estimated IQs and Ws are given in table IV.

TABLE IV
RANK CORRELATIONS (ρs) BETWEEN ESTIMATED IQ AND EEG FREQUENCY-PATTERN VARIATION (Ws) FOR 6 FREQUENCIES

IQ, W(LO-E)	.054
IQ, W(LpC-E)	.0046
IQ, W(LO-P)	.213
IQ, W(LO-pC)	.125

Although one is higher than any of the previously obtained correlations (table II), none are significant and they are in the wrong direction as far as the hypothesis being tested is concerned.

DISCUSSION

We have failed to substantiate the hypothesis of a relationship between EEG frequency-pattern variation and test intelligence. The most obvious inference to be drawn is that there is no relationship between EEG frequency-pattern variability and test intelligence, but there are other possible explanations of our results. One is that, since we have not exhausted the possible combinations of

[1] We intended to use only 6 epochs for the analysis as Walter evidently did, but found that with our data, the reliability coefficient dropped to .57 ($P < .01$). Using 10 epochs the reliability coefficient was .72 ($P < .001$); compare with .87 for 14 frequencies over 10 epochs.

electrode pairs, we may have missed areas of the brain which would yield the sought-for relationship; but since our results are uniformly negative, and since significant correlations were found among the areas we did study, we would not feel optimistic about obtaining positive results with other electrode pairs.

A second possible explanation is that our sample of subjects was somehow a biased one. It *was* biased in that it was a group of above average intelligence (mean IQ 116.9), but the range of IQs (64-147) and the standard deviation (18.2) were sufficiently great that the low correlations between estimated IQ and Ws do not seem reasonably attributable to homogeneity of IQ. On the other hand, W scores did appear somewhat homogeneous, and this may have contributed to the low correlations, but we have no way of knowing at the moment whether our sample was more homogeneous in this respect than the population of normal young adults from which it was drawn. We *do* have evidence that age was not a contributing factor. Correlations between age and estimated IQ ($\rho = -.15$) and age and EEG frequency-pattern variation ($\rho = -.07$) were low and not significant.

Inspection and spot-checking of the raw data indicate that there would have been no change in the results if we had ranked all 24 frequencies represented in the frequency analyses rather than the 14 or 6 we did use, nor any change if we had used only 6 epochs rather than 10 in deriving Ws.

These results suggest that the Wechsler-Bellevue scale is not a good measure of what Walter refers to when he uses the term "brilliance". Walter's concept of "brilliance", as nearly as we can gather, seems to include intellectual capacity or a variety of abilities and aptitudes plus some motivational factors, resulting in the display by the subject of diverse, broad interests and achievements. We felt that an intelligence test should be a measure of at least one component of "brilliance", and if so, there should be some correlation between intelligence test scores and EEG frequency-pattern variability, even if not a high one. We chose a widely used, standardized, objective test of intelligence, so that if positive results were obtained, a useful and widely applicable tool would be available for further investigation. Our negative results indicate that our expectation was wrong, and it is unlikely that other standard intelligence tests would yield positive results where the Wechsler-Bellevue does not. An approach from another direction would involve the assessment of "brilliance" in terms of its results, and this approach Walter has apparently already attempted.

On the positive side, we have been able to develop a reliable method for handling frequency analyser data, which yields a simple and statistically manipulable measure of EEG frequency-pattern variation, which can be applied to frequency bands of any width,[1] and which may be useful in future research in this area.

SUMMARY

An experiment was performed to test a hypothesis, suggested by Walter's work, that there is a relationship between test intelligence and EEG frequency-pattern variability. This involved the application of the coefficient of concordance (Kendall's W) to frequency analyser data to yield a single summary measure of frequency-pattern variability. The hypothesis was not confirmed.

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[1] It is to be noted, however, that the narrower the frequency band used the lower the reliability of measurement will tend to be.

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THE EFFECT OF CHLORPROMAZINE AND RESERPINE ON SEDATION AND CONVULSIVE THRESHOLDS IN SCHIZOPHRENIC PATIENTS

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(Received for publication: March 9, 1957)

INTRODUCTION

One of the earliest known properties of chlorpromazine was that, in common with other anti-histamine compounds, it potentiated the effects of central depressant drugs and was found to be more powerful in this respect than its analogues. Much of the evidence has been derived from animal experiments, however. Courvoisier *et al.* (1953) found that the sleeping time of mice, guinea pigs and dogs, injected with hexabarbitone, was markedly increased when they were pretreated with chlorpromazine. Kopera and Armitage (1954), using pentobarbitone, observed similar effects in mice. In man, chlorpromazine alone, or in combination with promethazine, has been given in preparation for general anaesthesia and the quantity of barbiturate reduced (Dobkin, Gilbert and Lamoureux 1954). A potentiation of the barbiturate sleeping time in experimental animals has also been reported with reserpine (Shore, Silver and Brodie 1955). There are on the other hand, reports of convulsions in patients treated with chlorpromazine and reserpine (Hollister *et al.*, 1955; Schlichter *et al.* 1956) and of an increase in convulsions in patients with convulsive disorders (Bonafede 1955; Barsa and Kline 1955; Faurbye 1955).

There seem to be some indications therefore, that these two drugs, chlorpromazine and reserpine, not only potentiate the action of central depressant drugs, but may also increase convulsions. Since there was in the hospital a large-scale clinical investigation in progress with these drugs, and since the methods for determining quantitatively the sedation threshold (Shagass 1954) and the convulsive threshold (Ulett *et al.* 1955) were already available, it was thought that an investigation into the effects of both chlorpromazine and reserpine on these thresholds in a group of chronic psychotic patients might throw further light on their action in man. In addition it was considered that the method of studying the effects of one drug, whose action was not fully known, in combination with another, whose effects are known and can be estimated quantitatively, might prove to be a useful one for investigating the effects of new drugs in psychiatric patients. Such a method has recently been successfully employed in the study of the effects of drugs in conscious animals (Bradley and Hance 1955, 1957).

METHODS

I. *Selection of Patients.* The group of patients chosen for this investigation consisted of chronic catatonic schizophrenics. This was done in order to obtain as homogeneous a group as possible with the minimum amount of doubt over diagnostic category. The patients chosen were either in stupor, semi-stupor or had had definite stuporous episodes. It is nevertheless impossible to standardize an investigation with schizophrenics owing to the liability of the symptoms to fluctuate and the behavior to vary from day to day and from week to week. Although 20 patients were originally selected, only 11 finally proved suitable, 4 of these being male and 7 female.

II. *Plan of Investigation.* The method used was to establish the control sedation threshold and control convulsive threshold in each patient and then to repeat these, first

after pre-medication with chlorpromazine, and then following reserpine. The doses of the two drugs were based on the clinical findings in the large-scale hospital trial and

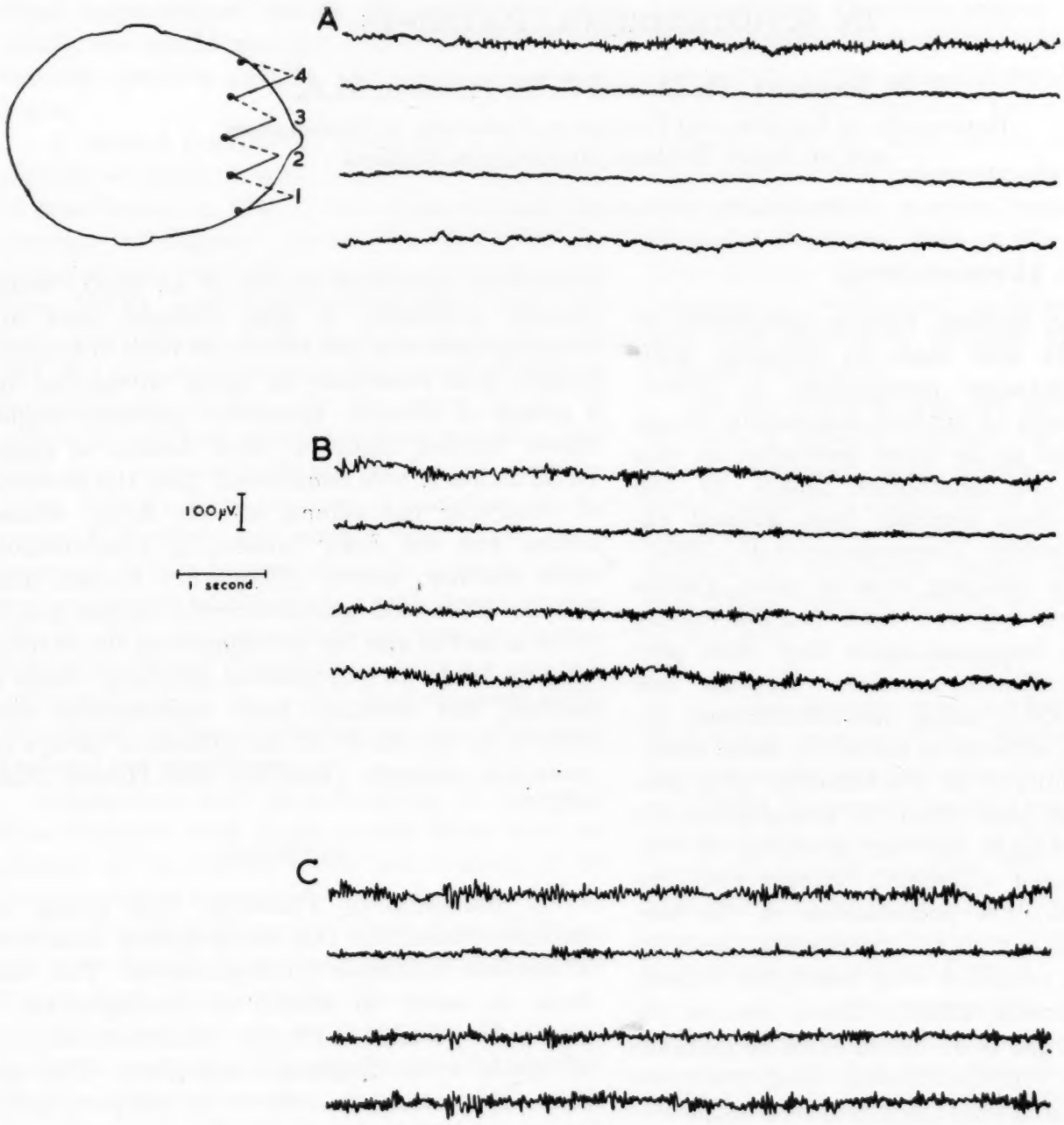

Fig. 1

EEG records of a female patient (G.P.) age 70, obtained whilst establishing the sedation threshold. A: before the injection was started, B: after 6 ml. and C: after 14 ml. of sodium amytal solution.

were chosen so that the two drugs should have a comparable clinical effect.

The method of administration of chlorpromazine was to give 50 mg. intramuscularly at 8 a.m. and again at 8 p.m. on the day before the experiment and a further 50 mg. one hour before the recording was started. The same procedure was used with reserpine but in this case the dose was 2.5 mg. for each intramuscular injection. None of the patients had received any treatment with drugs for several months before the investigations was started.

III. *Sedation Threshold.* It was originally intended that the method of Shagass (1954) should be used for establishing the sedation threshold. This consists of injecting a solution of sodium amytal containing 0.5 mg. per

kg. of body weight per ml., intravenously at a rate of 1 ml. every 40 sec. A clinical threshold is established by noting the quantity of sodium amytal required to produce slurring of speech, and the EEG threshold is obtained by plotting the amplitude of the fast activity induced by the drug.

It became immediately apparent that the clinical side of the method was unsuitable for our patients, if not for many chronic psychotic patients, since they were either mute or relatively inaccessible. The first modification in the method was therefore to establish a reliable *objective* clinical threshold which could be used with these patients.

In preliminary trials it was found that there was a number of objective changes, such as the closing of the eyes which had remained persistently open, or the falling back of the head onto the pillow in patients who adopted the classical catatonic posture when lying down. These changes were very variable, however, and were not found to be sufficiently reliable. The only clinical threshold which

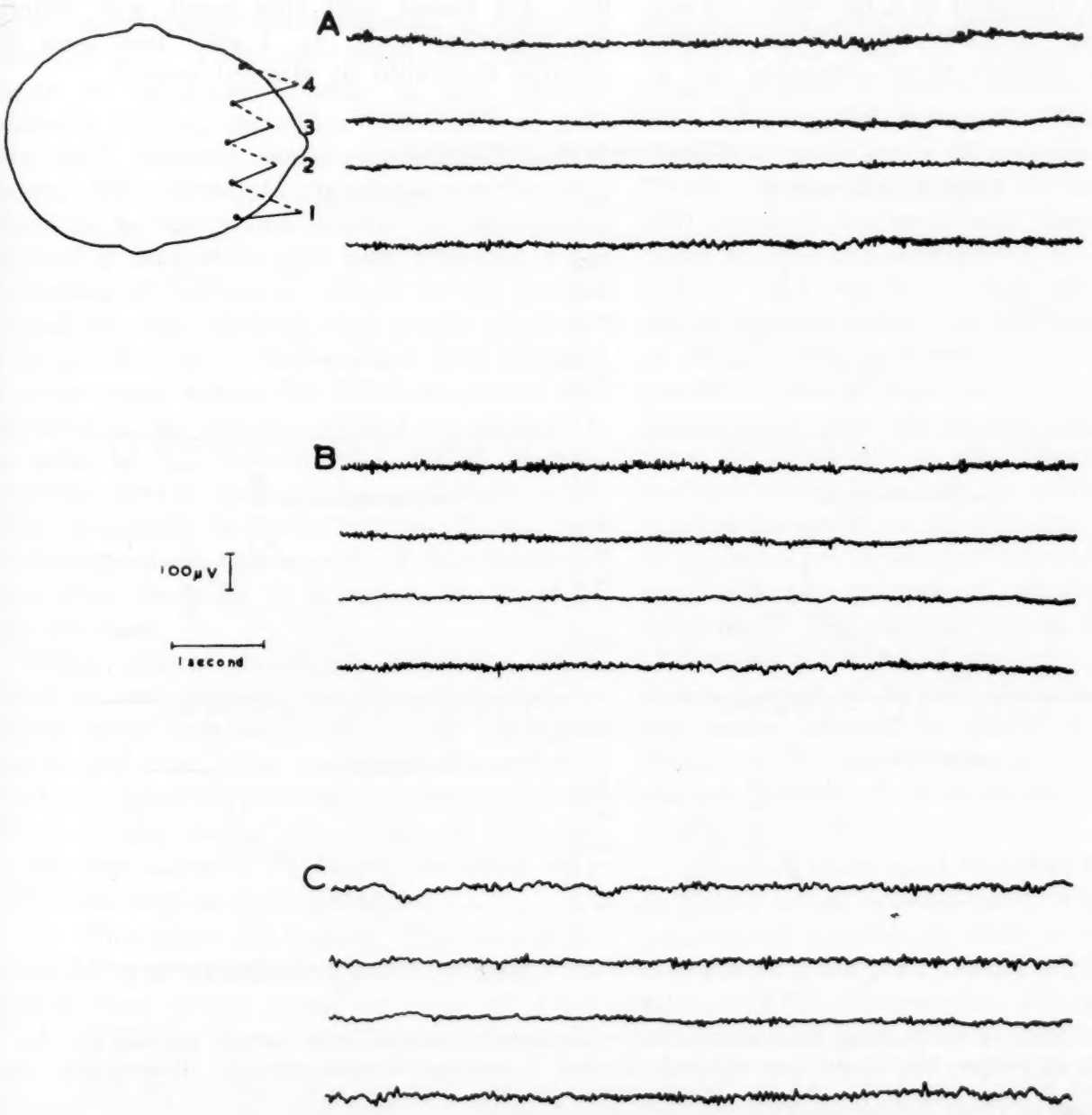

Fig. 2

The same as figure 1 but in a different patient (W.H., female, age 45).

could be assessed with any reasonable accuracy was that of sleep, as shown by a failure to respond to a verbal command to open the eyes. Trials showed that injecting 1 ml. of sodium amytal solution every 40 sec. did not always result in sleep and the rate of injection was therefore increased to 1 ml. every 30 sec. The maximum quantity of sodium amytal given to any patient never exceeded 0.5 g.

by measuring the amplitude of the fast activity induced by the barbiturate and plotting this against the quantity of amytal injected. This amplitude, according to Shagass, rises rapidly to a peak and the graph then flattens, the point of inflection being the EEG threshold. He found that this point was usually one injection unit (ie. 1 ml.) less than the clinical threshold of slurred speech.

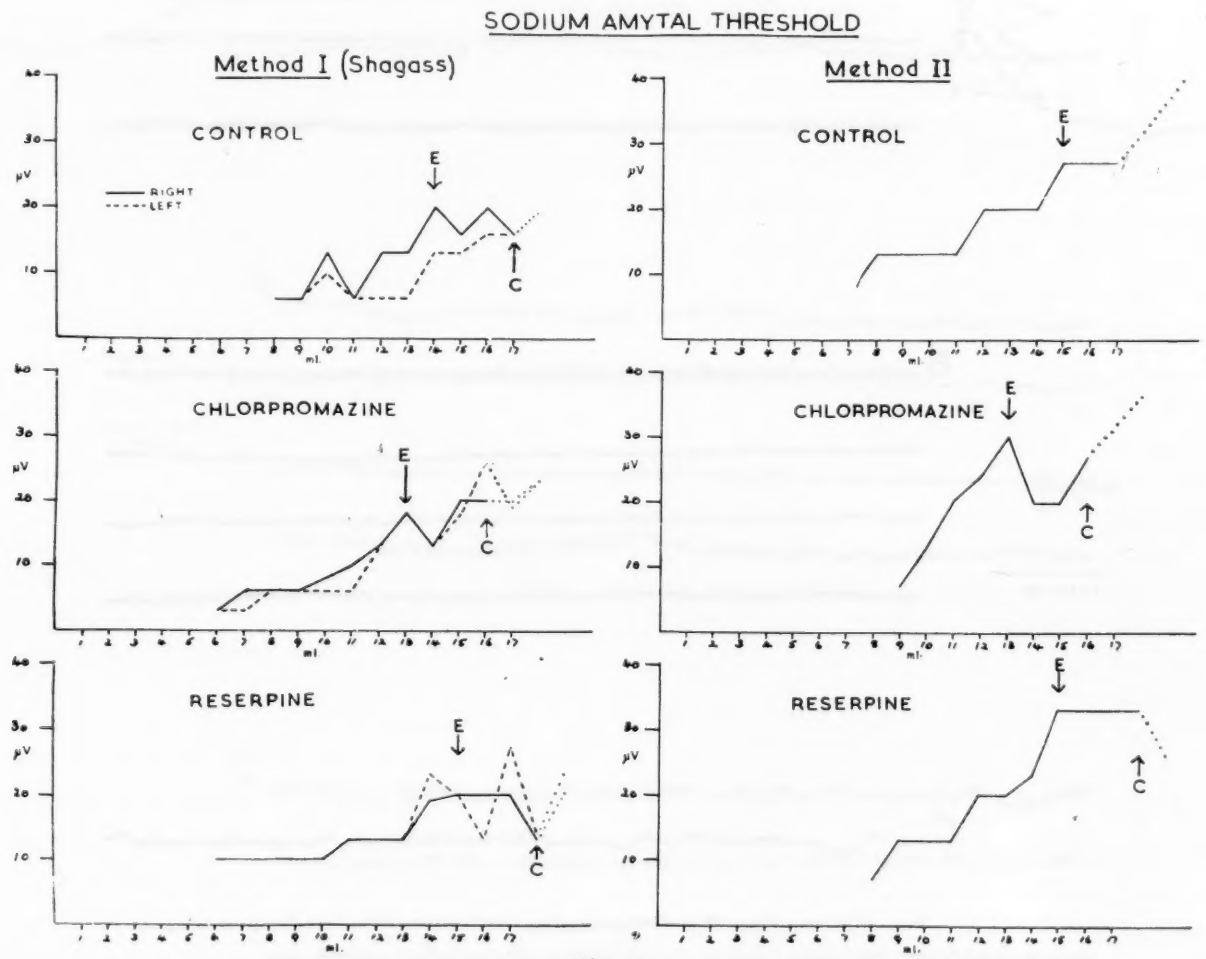

Fig. 3

Graphs obtained by plotting the amplitude of fast activity in the EEG record against the quantity of sodium amytal solution injected. Method I, original Shagass method. Method II, modified method (see text). All the graphs were obtained from the same patient (W.G.P.) and a total of 17 ml. corresponded to 0.5 g. of sodium amytal.

Ten seconds after each injection the command to open the eyes was given and if there was no response it was repeated in a louder voice after the next injection. In a few cases, because of negativism or inaccessibility, other signs were used to confirm the clinical threshold.

Shagass correlated the clinical threshold with the EEG threshold which was obtained

The Shagass method for establishing the EEG threshold was adopted but it was found to be difficult technically and liable to inaccuracies, especially in low voltage records (compare fig. 1 and 2). The graphs were plotted by the EEG recordists and examined independantly by each of the authors. This was done by one of us (P.B.B.) without knowledge of the clinical threshold. It was found

to be very difficult in most cases to distinguish any definite point of inflection on the curves (fig. 3, method I). Because of this difficulty further graphs were plotted in many cases, using several different methods. These all showed the same basic pattern however, and samples of one of these methods are shown in the right-hand column in figure 3 (method II). They are based on measurements of amplitude made in the fronto-temporal region, on either the right or left side, and include measurements of single waves. The threshold on these graphs was taken to be the point where the amplitude reached a maximum and was followed by a flattening of the curve. Since in the graphs plotted by this method, this point appeared to be much clearer, the method was adopted in those cases where the EEG threshold was doubtful in the graphs plotted by method I. In spite of the inaccuracies which became apparent in the method for establishing the EEG threshold for sedation, we found that our independant assessments of this threshold were often the same or varied at the most by only one unit.

When control thresholds had been established in each patient, the procedure was repeated after pre-medication with chlorpromazine and then after reserpine. In order to avoid any possibility of the persistence of the effects of any one of the drugs, at least one month was allowed to elapse between each individual test in each patient.

IV. *Convulsive Threshold.* The convulsive threshold was established with hexazol, the method used being based on that of Ulett *et al.* (1955). Three preliminary methods were tried and abandonned. The first was identical with the method used by Ulett and his co-workers and consisted of injecting 1 ml. of a solution of hexazol (5 mg/ml.) over a period of 10 sec., then pausing for 10 sec., followed by photic stimulation at 15 flashes/sec. for a further 10 sec. The whole procedure was then repeated until the threshold was reached. This method was given only a few trials because it was found that the end point was reached after only 5 or 6 injections, and it was felt that this was too rapid to enable a small change in threshold to be detected. In addition, one patient had a convulsion shortly after the end of the recording and another appeared to be ill, and it was thought that insufficient time was being allowed between successive injections for the drug to exert its full effect. The next step was, therefore, to increase the interval between the injections and this was done by interposing two additional periods of photic stimulation, with 10 sec. intervals in between. Thus, injections were now made every 60 sec. instead of every 20 sec. It was found that the end point was still reached too soon and therefore in the third method the strength of the solution was halved (2.5 mg/ml.), but when this was tested, no end point was reached. With both of these methods it was seen that the third period of photic stimulation evoked no more abnormality than the second and could therefore be omitted. In the fourth and final method, which was used to establish the convulsive threshold in all patients, the strength of the solution of hexazol was made 4 mg/ml. and only two periods of photic stimulation were used. The method was as follows: 1 ml. of hexazol solution (4 mg/ml.) was injected over a period of 10 sec., then there was a 10 sec. pause, followed by photic stimulation for 10 sec., a further 10 sec. pause and another similar period of stimulation, followed immediately by the next injection.

The end point used was that recommended by Ulett *et al.* (1955) and was either (*a*) generalized myoclonus, with or without EEG abnormality or (*b*) facial twitching with marked EEG abnormality, usually consisting of spikes and slow waves. The most common finding was that of generalized myoclonus, with spiking and slow waves in the EEG, but the precise nature of the end point was not always the same even in the same patient. When there was any doubt about the threshold the test was repeated at a later date. In some cases spontaneous abnormalities occurred and these made it more difficult to establish the threshold. Three patients showed these abnormalities quite consistently and to a marked extent. Two examples from one patient are shown in figure 4 and it can be seen that their

occurrence may be completely unrelated to the photic stimulation and can, in fact, precede it.

One patient had a major fit on two out of three occasions, with no spontaneous abnormality and no clinical warning. This patient was excluded from the series as he was ill for several days after each fit. Another patient became extremely frightened as the threshold was reached and sat up suddenly, pulling off the electrodes. This happened on two occasions when he had been pre-treated with chlorpromazine, but not in the control test or after reserpine. It was not possible to obtain any subjective information from this patient as he was quite mute. In most cases, because of apprehensive appearance or the presence of spontaneous abnormalities in the EEG record or, if the total dose of hexazol had been large, the patient was given a rapid intravenous injection of 2.5 g. of sodium amytal immediately after the convulsive threshold had been established.

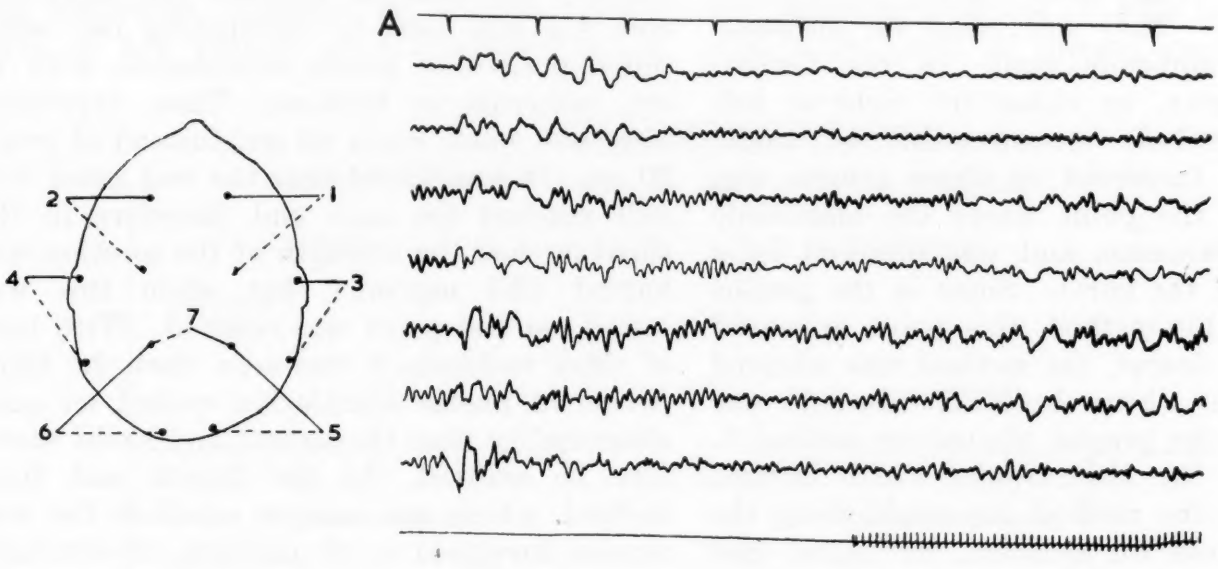

Fig. 4

EEG records obtained in establishing the convulsive threshold in a female patient (M.J., age 38), showing the presence of spontaneous abnormalities. A: the spontaneous abnormality is larger in amplitude than that occurring during photic stimulation (stimulus marker in bottom trace). B: another spontaneous episode in the same patient.

RESULTS

I. *Sedation Threshold.* The sedation thresholds established with sodium amytal, both in the normal and after chlorpromazine and re-

serpine, are shown for each patient in table I. The clinical and EEG thresholds are given separately in each case and the units correspond to the number of ml. of solution injected.

It can be seen that in 4 patients (W.G.P., I.S., S.P. and M.G.) there was a considerable discrepancy between the clinical and EEG thresholds in the normal, but this is perhaps not unexpected since the clinical threshold used was that of sleep and not of slurring of speech. This discrepancy was maintained in these patients after chlorpromazine had been given and in 2 (W.G.P. and I.S.), it was also maintained after reserpine. In one (M.G.) the clinical and EEG thresholds were the same after reserpine and in the other (S.P.) it was not possible to measure the EEG threshold. Three patients (T.B., J.S. and I.O'D.) did not sleep when the control sedation threshold was being established and therefore no clinical threshold was obtained for these. The other 4 patients showed a fairly close agreement between clinical and EEG thresholds.

TABLE I

SEDATION THRESHOLDS

Patient		Normal		Chlorpromazine		Reserpine	
		Clin.	EEG	Clin.	EEG	Clin.	EEG
T.B.	(M)	—	15	15	14	10	9
W.G.P.	(M)	17	14	16	13	18	15
G.R.	(M)	18	16	16	9	15	12
I.S.	(M)	16	11	16	11	18	9
J.S.	(F)	—	11	15	12	18	18
M.J.	(F)	15	15	15	12	16	15
S.P.	(F)	17	13	13	11	16	—
W.H.	(F)	11	11	16	12	12	12
I.O'D.	(F)	—	15	11	11	18	15
G.P.	(F)	14	14	10	9	13	14
M.G.	(F)	13	9	12	9	12	12

(*a*) *Following Chlorpromazine.* In 5 patients (G.R., M.J., S.P., I.O'D. and G.P.) the EEG threshold for sedation showed a significant change following pre-medication with chlorpromazine. This was, in all cases, a lowering of the threshold, ranging from 2 units (S.P.) to as much as 7 units (G.R.) In 2 patients (J.S. and W.H.) there was a rise in threshold of one unit, and in another 2 (T.B. and W.G.P.) a fall of one unit, whilst in the others (I.S. and M.G.) the EEG sedation threshold remained unchanged. Thus, since only a change of 2 or more units was regarded as significant, the EEG threshold in 6 patients showed no significant change, but in 5 there was an appreciable decrease after pre-medication with chlorpromazine.

The control clinical sedation threshold could be established in only 8 patients. In 3 this threshold showed a fall of 2 or more units after chlorpromazine, and these patients (G. R., S.P. and G.P.) were ones in which the EEG threshold had decreased by a significant amount as well. In 4 patients (W.G.P., I.S., M.J. and M.G.) the clinical threshold did not change significantly, but in another (W.H.) there was a considerable increase in this threshold. In this patient the EEG threshold did not change appreciably.

(*b*) *Following Reserpine.* Following premedication with reserpine, the EEG sedation threshold showed, in 6 cases, either no change (M.J., I.O'D. and G.P.) or a change of only one unit (W.G.P. and W.H.). In 2 there was a significant increase in threshold (M.G., 3 units and J.S., 7 units) and in 3 others, an appreciable decrease (I.S., 2 units; G.R., 4 units and T.B., 6 units). In one patient the EEG threshold could not be measured after reserpine owing to the presence of persistent muscle artefact in the record which obscured the barbiturate fast activity.

The clinical sedation threshold showed no change in 6 patients. In 3 of these (W.G.P., M.J. and W.H.) there was a rise of one unit and in the other 3 (S.P., G.P. and M.G.) a fall of one unit. In one patient (I.S.) there was a rise in threshold of 2 units, but in this case there was a fall in the EEG threshold of a corresponding amount. Another patient (G.R.) showed a significant fall in the clinical threshold and in this case there was a fall in the EEG threshold as well. Unfortunately, with the 2 patients who showed the greatest change in the EEG threshold after reserpine, it had not been possible to establish a control threshold, as these 2 patients did not go to sleep.

II. *Convulsive Threshold.* The convulsive thresholds, established with hexazol, are shown for each patient in table II, both in the normal and after chlorpromazine and reserpine. The units, as with the sedation thresholds, represent the quantity of solution injected in ml. in each case. The control convulsive thresholds show a wide range of variation in these patients. In 2 (J.S. and M.J.) it was as low as 4 units and in one (T.B.) as high as 15.

(*a*) *Following Chlorpromazine.* In 6 patients (G.R., I.S., J.S., M.J., S.P. and G.P.) the convulsive threshold showed no change after pre-medication with chlorpromazine, and in a further 3 (W.H., I.O'D. and M.G.) the

TABLE II

CONVULSIVE THRESHOLDS

Patient		Normal	Chlorpromazine	Reserpine
T.B.	(M)	15	13	14
W.G.P.	(M)	5	7	6
G.R.	(M)	7	7	7
I.S.	(M)	8	8	8
J.S.	(F)	4	4	4
M.J.	(F)	4	4	3
S.P.	(F)	6	6	6
W.H.	(F)	5	4	5
I.O'D.	(F)	8	7	7
G.P.	(F)	5	5	6
M.G.	(F)	5	4	5

change (a fall) was only one unit and therefore not regarded as significant. In one patient (T.B.) there was a fall in threshold of 2 units, and in another (W.G.P.) a rise of 2 units. Thus after chlorpromazine, 9 patients showed no significant change in the convulsive threshold and 2 showed significant changes, one a rise and the other a fall.

(*b*) *Following Reserpine.* As with chlorpromazine, 6 patients (G.R., I.S., J.S., S.P., W.H. and M.G.) showed no change in their convulsive thresholds after pre-medication with reserpine. In another 3 patients (T.B., M.J. and I.O'D.) the threshold fell by one unit, and in a further 2 (W.G.P. and G.P.) it increased by one unit. Thus, with reserpine there were no significant changes in the threshold.

DISCUSSION

The results of all the experiments are summarized in table III. The figures here represent the number of patients in each group and only a change in threshold of two or more injection units has been regarded as significant. Thus patients with a change in threshold of only one unit have been included in the group showing no change.

As has already been stated, none of the patients in this series showed any significant change in convulsive threshold when pretreated with reserpine. Similarly with chlor-

TABLE III

		Convulsive threshold	Sedation threshold Clinical	Sedation threshold EEG
CHLORPROMAZINE	Increase of 3 or more	0	1	0
	Increase of 2 ml.	1	0	0
	Unchanged	9	4	6
	Decrease of 2 ml.	1	1	1
	Decrease of 3 or more	0	2	4
RESERPINE	Increase of 3 or more	0	0	2
	Increase of 2 ml.	0	1	0
	Unchanged	11	6	5
	Decrease of 2 ml.	0	0	1
	Decrease of 3 or more	0	1	2

promazine pre-medication, only 2 out of 11 showed any change in the convulsive threshold, and in these 2 the changes were opposite, one being a rise and the other a fall. It may therefore be concluded from these results that neither chlorpromazine nor reserpine appear

to have any influence on the convulsive threshold in chronic schizophrenic patients, as measured by this method. Convulsions have been reported in patients receiving these two drugs but an examination of these reports shows that where an increase in the number of fits occurred in epileptic patients, it might equally well have been due to a decrease in the amount of barbiturate given. It is to be noted that where the barbiturates remained at the same level, there was no significant increase in fits. Shea, Alman and Fazekas (1955), treating patients with head injury (including one epileptic patient) report no convulsions. Hollister *et al.* (1955) report that a combination of the two drugs increased the likelihood of convulsions, whilst Barsa and Kline (1955) found that the combination resulted in a lower incidence in convulsions than occurred with reserpine alone. The majority of reported cases of convulsions in non-epileptic patients have been associated with large doses of these drugs. If it is accepted however, that these two drugs can increase the incidence of convulsions, then a number of possible explanations for the present findings may be considered. Firstly, it might be argued that the method used here might not be sufficiently accurate to detect small changes in the convulsive threshold. Whilst this is possible, it it considered unlikely that such small changes in threshold could be responsible for the occurrence of spontaneous seizures. Secondly, the group of patients chosen for this study might represent a special group and may not be typical of those in which spontaneous seizures occur. A third possibility is that the doses of chlorpromazine and reserpine used in this investigation were too small to provoke either seizures or a change in threshold. It was intended, however, to use only normal clinical doses in this investigation. A fourth, and in our opinion more likely explanation, is that the mechanism by which seizures are produced in the combined hexazol-photic stimulation method might not be related to the mechanism of spontaneous seizures, and that whereas the results of our experiments would suggest that there is no interaction between either chlorpromazine or reserpine and hexazol, the first two drugs may still modify the threshold for spontaneous seizures in patients when given in sufficiently large doses.

Considering now the sedation thresholds, following reserpine there were appreciable changes in certain patients, but this was in some cases an increase and in others a decrease (table III). There were therefore no consistent changes in the sedation threshold in these experiments when reserpine was given and we have been unable to confirm in man the suggestion that this drug potentiates the action of barbiturates (Shore, Silver and Brodie 1955). In our opinion there was no evidence of an interaction between reserpine and sodium amytal with the doses used.

In the case of chlorpromazine there did appear to be some consistent changes in the sedation threshold and, with one exception, when the threshold changed, it showed a decrease. The exception was one patient (W.H.) in whom the clinical threshold increased, but the EEG threshold showed no significant change. In 3 of the patients in which the change in the EEG threshold was large enough to be regarded as significant, the clinical threshold changed as well. Of the others, there were 3 patients in which neither threshold changed. Thus, there is some evidence from these experiments that chlorpromazine may in some cases lower the threshold for sedation produced by sodium amytal. Whether this can be regarded as a true potentiation of the effect of one drug by another is difficult to say. The fact that a smaller quantity of barbiturate is required to produce the same degree of sedation following chlorpromazine is perhaps only to be expected from the increased degree of relaxation produced by the latter drug, and from its possible site of action in the central nervous system (Bradley and Hance 1955, 1957; Bradley and Elkes 1956). This idea is further supported by the changes which were observed in the resting records of the patients treated with chlorpromazine. The control resting records of the patients used in this investigation showed low voltage, fast activity, with very little if any alpha activity, but considerable muscle artefact (fig. 5 A). This type of record, which

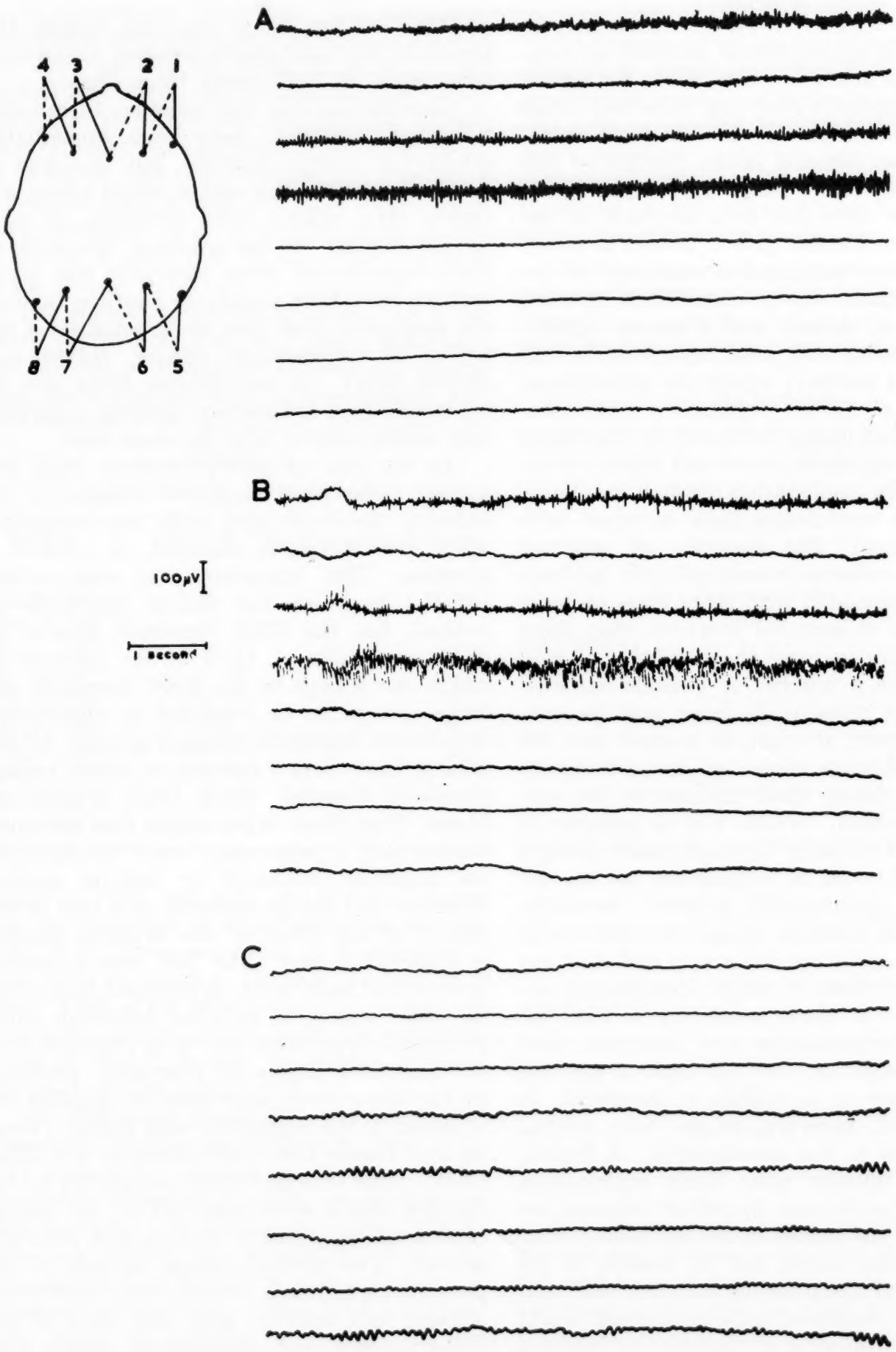

Fig. 5

Resting EEG records of the same patient (I.S., male, age 30), A: before any medication, B: after pre-medication with reserpine (2.5 mg.) and C: after chlorpromazine (50 mg.).

is common in schizophrenics and probably reflects a state of tension, was seen in 8 out of the 11 patients. After chlorpromazine, there was in all 8, an increase in the amplitude of the activity and a decrease in muscle artefact, together with the appearance of some alpha activity (fig. 5 C). This type of change in the resting record was not seen with the doses of reserpine used here (fig. 5 B), but has been observed with large doses (up to 18 mg. daily). Patients receiving these large doses of reserpine often showed symptoms of parkinsonism and quite frequently there was theta activity present in their EEG records.

Both of the methods by which it had been proposed to establish the thresholds had to be modified before they could be used. The convulsive threshold was found to be fairly easy to establish accurately, and the changes which had to be made in the method were probably related to the type of patient used in this investigation. With regard to the method for establishing sedation thresholds, it is felt that this has to be used with care in patients incapable of full co-operation.

SUMMARY

1. The effects of chlorpromazine and reserpine, in normal clinical doses, on both sedation and convulsive thresholds have been studied in a group of eleven chronic catatonic, schizophrenic patients.

2. The sedation threshold was determined by injecting sodium amytal intravenously, the method being based on that of Shagass (1955). Because of the inaccessibility of the patients, a clinical threshold of sleep was used. The method of assessing the EEG threshold was modified in many cases as the original method did not give clear results.

3. The convulsive threshold was determined by injecting hexazol intravenously, the method being based on that of Ulett *et al.* (1954). It was found necessary to modify the method as the end-point was reached after too few injections and the drug appeared to have a delayed effect, resulting in convulsions after the test was finished.

4. The thresholds were determined in the normal and after pre-medication with: (*a*) chlorpromazine and (*b*) reserpine. Following reserpine, in normal clinical doses, neither the sedation threshold, nor the convulsive threshold showed any significant change. The same was true of the convulsive threshold after pre-treatment with chlorpromazine.

5. After chlorpromazine there were significant changes in the sedation thresholds in a number of patients. These changes were consistent, being a lowering of the sedation threshold. The relation of these findings to the possible mode of action of the drugs and the reports of the occurrence of spontaneous seizures when they are used, is discussed.

We wish to thank Professor J. Elkes for his advice and encouragement of this work and Dr. J. J. O'Reilly for providing the facilities and for permission to publish this paper. We are also very much indebted to our two recordists, Miss Ursel Stinnes and Miss Mary Dyas who, apart from taking all the records, undertook the tedious work of measuring the amplitude of the activity and plotting the graphs for the sedation thresholds.

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CYCLIC VARIATIONS IN EEG DURING SLEEP AND THEIR RELATION TO EYE MOVEMENTS, BODY MOTILITY, AND DREAMING

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INTRODUCTION

The EEG patterns accompanying dreaming have never been adequately characterized. In the course of the early descriptive studies of sleep patterns, incidental observations were made by several different groups of investigators and their combined results seemed to indicate that dreaming could occur in all stages of sleep. Davis *et al.* (1938) got reports of dreaming from subjects who were awakened shortly after the onset of sleep when the EEG had not progressed beyond the "B" stage, a low voltage, irregular pattern, and also after awakening from a "C" stage, spindling with a low voltage background. Blake, Gerard, and Kleitman (1939) concluded that "dreaming is present most of the time" mainly on the basis of one subject who reported dreams nearly every time she was awakened during the night. They felt that dreams were less likely to occur in the presence of high voltage, delta activity. Knott, Henry, and Hadley (1939), on the other hand, obtained several reports of dreaming when subjects awakened spontaneously during periods of high voltage delta activity, and also during spindle activity. Henry (1941) described dreams reported after awakening from low voltage, spindle, and spindle plus delta stages. In a study specifically concerning the relation between EEG patterns and dreaming, Teplitz (1943) concluded that dreams could occur in association with any sleep potential pattern, but found the highest incidence of dream recall after awakenings during the "B" and "C" stages.

The above results, frequently cited in the literature, suggest a lack of relation between EEG stages during sleep and functional levels of central nervous activity. However, dreaming, with its complex visual imagery and at least a certain degree of organization and purposefulness, is closely akin to waking mental activity, and the supposition that it can occur at any level of sleep as indicated by brain waves is difficult to accept. To be sure, with the exception of Teplitz, the dream reports in the studies cited above were very small in number.

A new method for the detection of dreaming was recently described by Aserinsky and Kleitman (1955a) who reported the occurrence of periods of rapid conjugate eye movements during sleep and found a high incidence of recall of dream content in subjects awakened during these periods and a low incidence after awakenings at other times. The occurrence of these eye movements and their relation to dreaming was confirmed in both normal subjects and schizophrenics (Dement 1955), and a recently completed study appears to have conclusively established this relationship (Dement and Kleitman 1957). In this study, an 80 per cent incidence of vivid detailed dream recall was elicited from subjects after nearly 200 awakening during periods of rapid eye movements over many nights of sleep. Adequate control was maintained throughout the experiments of such distorting factors as the subjects' desire to please the experimenter with dream reports and unintentional cuing by the experimenter. Only 7 per cent recall was obtained after a comparable number of awakenings, randomly interspersed, when the eyes were quiescent. It was noted that the largest share of these dream reports during quiescent periods re-

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sulted from awakenings following very soon after the end of a rapid eye movement episode which suggested that they resulted from the persisting memory of earlier dream material rather than dreaming during the quiescent periods. In addition, it was demonstrated that the subjective estimation of dream-duration and the amount of dream narrative correlated highly with the length of the rapid eye movement period before awakening, and that the eye movements themselves seemed to be meaningfully related to the visual imagery of the dream. Brain waves were recorded, and it appeared that the eye movement periods were associated with a low voltage pattern while the interspersed periods of ocular quiescence were associated with spindle and delta stages.

In the investigation to be described, the EEG during *undisturbed* all night sleep was carefully examined using the periods of rapid eye movement as an objective criterion of dream activity. In this way it was hoped to establish conclusively that the rapid eye movements (dreaming) were associated with a characteristic EEG stage and to determine the frequency of occurrence and quantity of rapid eye movement and related EEG variations throughout an entire night of sleep. Body movement was also observed because of its possible relation to dreaming and its close association with EEG changes during sleep.

Some of the data have already been described in a brief preliminary report (Dement and Kleitman 1955).

SUBJECTS AND METHOD

The subjects for the experiments were 26 men and 7 women. Their ages ranged from 16 to 61 with the majority between 20 and 30. All gave negative medical histories and none reported having insomnia or other sleep difficulties.

All night recordings of eye movements, brain waves and body motility were made on each subject for one or more nights of sleep. In a typical experiment, a subject reported to the laboratory a little before his accustomed bedtime. He had been previously requested to abstain from coffee, alcohol, excessive food intake, and unusually strenuous exercise during the day. Silver disc electrodes were affixed to the scalp with collodion and to the ear lobes and around the eyes with elastoplast. Great care was taken in attaching the electrodes so that they would remain in place without drying throughout the entire night. The lead wires were gathered together and further fastened to the top of the head with collodion. The subject then went to bed in a quiet dark room. The leads were taped together and ran as a single cord to the lead box at the head of the bed. This arrangement allowed a free range of movement without entanglement and minimized any annoyance to the subject. The experimenter then retired to an adjacent room where the recording equipment was located and did not again enter the experimental room or disturb the subject in any way until he awoke spontaneously in the morning or until his sleep was terminated artificially after an adequately long period.

The EEG and eye movement potentials were amplified and recorded by a four channel Grass Model III Electroencephalograph. All pens were set at the same gain and the EEG time constant was used throughout. Monopolar recording, either from scalp or eyes, was with reference to both ear lobes. In the first few experiments, one channel recorded the EEG monopolarly usually from a parietal electrode and three channels were used for eye movement potentials. One pen gave a bipolar record from a supra-orbital electrode above one eye to an infra-orbital electrode. The other two pens recorded monopolarly from the same two orbital leads referred to the ear lobes. Changes in the resting potential field, with reference to the electrodes, as the eyeball rotated were assumed to generate the observed electrical impulses (Fenn and Hursh 1937). In this way it was felt that eye movement potentials could be accurately differentiated even in the extreme case of a very small movement against a high voltage EEG background. Brain waves, with the same gain on all pens, were of smaller amplitude with the bipolar arrangement (supra-orbital to infra-orbital) than with the monopolar, and were also in phase on the monopolar pens. Consequently, only eye

movements gave the characteristic criteria of larger deflections on the bipolar pen and simultaneously out of phase smaller deflections on the monopolar pens. Vertical eye movements gave the largest potentials and movements in other directions varied approximately as the cosine of the angle of displacement from vertical.

It soon became apparent that such careful recording of eye movements was not necessary and subsequently they were recorded with either two pens monopolarly or one pen bipolarly allowing more pens to be used for EEG tracings. Also horizontal eye movement leads were frequently used, one on each outer canthus, because of the ease of their attachment. These gave the same differentiation criteria as the vertical leads. The usual technique was to definitely ascertain the presence of eye movements and then quickly switch so that three pens recorded the EEG from frontal, parietal, and occipital leads referred to the ears and one pen recorded from the eye bipolarly.

Electrode resistances were checked before the subject retired and any electrode giving a reading above 10,000 ohms was re-applied. The resistances were then checked at the Grass machine irregularly throughout the night and it was found that they invariably remained less than 10,000 ohms.

Body motility was recorded by means of an attachment to the bed spring which registered a deviation on a moving tape when the subject stirred. Note was also made of body movement artifacts in the EEG record and the two sources were combined to give the final motility record.

The EEG machine was run continuously throughout the night. This was important because the EEG changes and eye movement periods frequently lasted only a few minutes and might have been missed entirely by intermittent sampling. A constant paper speed of the standard 3 cm. per sec. was impossible because of the prohibitive quantity of paper that would have been consumed in the 6-8 hours of recording. Therefore, whenever possible, the paper speed was slowed to 0.6 or 0.3 cm. per sec. The reliability of doing this was greatly enhanced by the fact of the experimenter's constant attendance, because the paper speed could be immediately increased when any change occurred or any question arose. Also, frequent confirmatory standard speed samples could be taken.

High voltage delta waves were easily identified at the slower speeds due to their wide amplitude band. Low voltage faster waves required a standard speed most of the time, but spindles with a moderate amount of delta activity could be identified at the slower speeds because of the wider band and because the experimenter could actually see and hear the characteristic movement and scratch of the pens while reproducing a spindle and could confirm this impression with frequent standard speed samples. The records were all carefully measured and judged at a later date in addition to the original on-the-scene judgments.

In order to facilitate the organization and analysis of the large amount of data from many experiments running continuously for hours, the categorization of the EEG patterns during sleep was somewhat simplified. Four categories or stages were used:

Stage 1. The essential characteristic was an *absolute lack of spindle activity.* In general, a low voltage, relatively fast pattern corresponding to the "B" stage of Loomis *et al.* (1937) and the "drowsy" stage of Gibbs (Gibbs and Gibbs 1950), and including what the Loomis group called the "A" or interrupted alpha stage. Thus, any EEG pattern between full wakefulness and the appearance of spindles was included in stage 1.

Stage 2. Characterized by the presence of spindle activity with a low voltage background. A certain amount of slower activity was included in this stage in the 3-6 per sec. range. Gibbs' biparietal hump phase was also included although recognition of the humps was hindered by the unilateral recording. However, since this wave form is less prominent in the adult age group (Gibbs and Gibbs 1950) and in most cases was followed almost immediately by the appearance of spindles, its inclusion was felt justifiable. Careful distinction had to be made between spontaneous "K" complexes occurring in this stage and delta waves appearing in deeper

stages. In general, the "K" complex or arousal response could be easily identified by its wave form and its widely spaced occurrence which caused it to stand out sharply against the low voltage, spindle background.

Stage 3. An intermediate stage characterized by the appearance of high voltage slow waves with some spindling superimposed. In borderline cases, records with an average of less than two waves over 100 μV. and 1-2 c/sec. or slower in 10 sec. were assigned to stage 2 and records with more than half over 100 μV. and 1-2 c/sec. or slower were assigned to stage 4.

Stage 4. At least half or more of the record dominated by waves of 100 μV. or greater in the 1-2 c/sec. range or slower.

It should be emphasized that judgment was based on a fairly long stretch of record. Thus, if classifications were made of every few seconds of record, for example during a spindle stage, a spindle wave form might not occur in this brief period and the low voltage background would have to be assigned to stage 1. This would give the misleading impression of excessively frequent alternation between stages. Also, there was some tendency for delta waves to wax and wane and a few seconds of record during a waning phase would then have to be assigned to a different stage. In general, the judging of the record was a continuous, on-the-scene process.

RESULTS

I. The occurrence and interrelations of rapid eye movements, brain wave patterns, and body motility during a night's sleep.

In the first series of experiments, a total of 71 nights of sleep recordings was taken from 26 men and 7 women. The number of nights slept by each subject ranged from 1 to 7 with the majority being studied for 2 nights. The length of the sleep period averaged 6.5 hours and ranged from 2 to 9. In general, sleep was continuous except for occasional brief awakenings indicated by the appearance of a waking EEG pattern which usually followed gross body movements. These brief awakenings, as a rule, were not recalled by the subjects on the following morning. For purposes of analysis, if the awakening was prolonged more than a few minutes, the sleep period was considered terminated. Awakenings lasting more than a few seconds were easily identified by, in addition to the waking EEG, persistent muscle potential and movement artifacts, blink artifacts, and often the subject's calling out. The occasional brief bursts of waking EEG following body movements did not show these artifacts.

A. *Eye Movements.* Discrete periods during which their eyes exhibited rapid movements were seen in all 33 subjects every night they slept. The recorded eye movement potentials varied from just discernible up to several hundred microvolts. From controls it was seen that a 100 μV. deflection corresponded roughly to a movement through a 20 degree arc in the plane of the electrodes. A single movement was executed in about 0.1-0.2 sec. and was followed by a fixational pause of varying duration. Several experiments with electrodes around both eyes confirmed that the movements were binocularly synchronous and that they occurred in all directions. The size, direction, and amount of the movements varied widely and irregularly from moment to moment and period to period. In general, the movements tended to occur in clusters which were grouped together into a rapid eye movement period. However, the movement was sometimes virtually continuous throughout such a period and at other times exceedingly sparse. As a rule, the relative quiescent intervals between clusters of movement varied from several seconds to several minutes. Quiescence of more than 5 min. almost invariably signaled the end of a rapid eye movement period, and then no movements were seen until the onset of the next period. Figure 1, A-C, presents examples of eye movement potentials recorded at a slow speed from the outer canthi of one subject on the same night to illustrate variations in quality and quantity. Figure 1, D, is the occipital EEG band during an eye movement period from the same subject to show relative voltages. The eye movement potentials in figure 1, E, were recorded from the subject the next morning while he was sitting erect watching the experimenter. He was told not to move

his head but did not know his eye movements were being recorded. This record indicates that the potentials of purposeful waking movements are comparable to those seen during sleep.

No rapid eye movements were seen during the onset of sleep in the subjects studied. Table I summarizes the data concerning successive eye movement periods throughout the night for this group of experiments. It should be noted from the mean durations that the eye movement periods tended to be longer the later in the night they appeared. In general, 4 eye movement periods were seen in 6 hours of sleep. Because of the small number of nights where sleep lasted longer than 6-7 hours only a few fifth periods were seen and in just one night's sleep lasting 9 hours was a sixth eye movement period observed. The shortest quiescent interval between eye movement periods was 36 min. The range of duration of eye movement periods was quite large, 1 to 72 minutes. The range of time of appearance after the initial sleep onset increased for each successive period due to temporal dispersion. Calculated on the basis of the first 6 hours of sleep, the average total time taken up by eye movement periods was 64 min. or 17.7 per cent. The percentage would, of course, be larger for sleep durations of 8 hours or more, since the longer eye movement periods generally occurred during the later portions of the night. For reasons to be discussed later, if sleep showed a persistent lightening at about 1 hour after the initial onset without the appearance of eye movements and then deepened again, the first eye movement period was tabulated with the group of second eye movement periods. This occurred in 15 of the 71 nights in records from 11 subjects.

Fig. 1

Sample tracings of eye movement potentials. A-C are bipolar records from the outer canthi of one subject on a single night. D is the monopolar occipital EEG coincident with B illustrating the low voltage EEG. E is a sample of eye movement potentials from the same subject after awakening in the morning.

A small series of control experiments was done to test the possibility that the lack of eye movement potentials at certain times was due to marked decrease of the resting potential of the eye. Subjects were awakened by a buzzer during these periods and according to previous instruction immediately began moving their eyes back and forth between two dim lights above the bed. In all cases, the eye movement potentials that appeared within 3 to 10 sec. after the onset of the noise were

comparable in amplitude to those seen during both sleep and wakefulness.

B. *Electroencephalographic findings.* The EEG showed a strikingly consistent relationship to the rapid eye movement periods. The only pattern seen while the eyes were moving was stage 1, a low voltage, non-spindling EEG. This stage invariably persisted throughout the entire eye movement period, including the intervals of relative ocular quiescence between clusters of movement, and also throughout the entirety of periods with very sparse amounts of movement. Rare exceptions to this occurred when the EEG changed briefly to stage 2 in the middle of an eye movement period. No actual eye movements ever coincided with the stage 2 EEG, however, and the reappearance of eye movements was always accompanied by a reversion to stage 1. This "slipping" down to stage 2, when seen, usually happened during the first eye movement period and almost never occurred later in the night.

TABLE I

TIME OF FIRST APPEARANCE AND DURATION OF SUCCESSIVE EYE MOVEMENT PERIODS

Eye Movement Period	Minutes after Sleep Onset		Duration	
	Range	Mean	Range	Mean
1st	45-118	67	1-36	9
2nd	107-222	156	2-54	19
3rd	180-340	253	4-72	24
4th	257-412	338	4-66	28
5th	300-420	404	30-39	34

The stage 1 EEG persisting throughout the eye movement periods showed considerable variation within this classification. Generally a low voltage, irregular pattern, there were also many bursts or trains of regular 7-10 per sec. waves in the occipital leads, and 18-25 or 5-7 per sec. waves in the frontals. Although all these variations were usually seen in every subject, the occipital regular waves were more common in subjects with a prominent waking alpha rhythm and were characteristically 1-2 c/sec. slower than the waking frequency. The frontal "beta" waves were more common in non-alpha subjects. These synchronous patterns were somewhat more prominent in the intervals between clusters of eye movements and often seemed to be disrupted or "blocked" by the eye activity. As far as could be seen, the EEG patterns accompanying an eye movement period 1 hour after the onset of sleep were no different from those accompanying eye movements 6 or 8 hours after the onset of sleep. Figure 2 contains sample EEG recordings taken on single nights from two subjects. It illustrates the stage classifications used in this study and particularly shows some of the various stage 1 patterns that occurred during the eye movement periods.

All the stage 1 EEG variations accompanying eye movements were also seen during the stage 1 EEG at the initial onset of sleep. The only distinction was that at the sleep onset the different patterns of the stage 1 classification appeared in a fairly orderly sequence as part of a steady progression from a waking EEG to deeper stages, whereas, during eye movement periods the stage 1 level was maintained for lengthy intervals, and variations within the stage occurred more or less at random.

The eye movement periods and sleep onset accounted for nearly all the stage 1 patterns. The only other times that they appeared in the records were: (*a*) following the cessation of eye movement periods but progressing quickly to stage 2; (*b*) often following large body movements for a few seconds; and (*c*) during the return to sleep after occasional brief spontaneous awakening. Of course, when the body movement or brief awakening occurred at a time when an eye movement period was about due, the stage 1 EEG could persist if rapid eye movements actually appeared. With the above exceptions, the interspersed periods of ocular quiescence were always associated with the "deeper" stages, 2, 3, and 4.

As the rapid eye movement periods occurred at regular intervals, so the EEG during the night showed a regular and concomitant variation. These regular sequences of variation were termed cycles. The definition of the first cycle was from the onset of sleep to the end of the first eye movement period, the second cycle was from the end of the first

eye movement period to the end of the second and so on throughout the night.

The usual sequence was that after the onset of sleep, the EEG progressed fairly rapidly to stage 4 which persisted for varying amounts of time, generally about 30 min., and then a "lightening" took place. While the progression from wakefulness to stage 4 at the beginning of the cycle was almost invariably through a continuum of change, the "lightening" was usually quite abrupt and coincident with a body movement or series of body movements. After the termination of stage 4, there was generally a short period of stage 2 or 3 which gave way to stage 1 and rapid eye movements. When the first eye movement period ended, the EEG again progressed through a continuum of change to stage 3 or 4 which persisted for a time and then lightened often abruptly with body movement to stage 2 which again gave way to stage 1 and the second rapid eye movement period. This cyclic variation in the EEG recurred repeatedly throughout the night. The slowest, highest voltage waves were usually seen in the first cycle and stages 3 and 4 were only occasionally reached during cycles following the second. As a rule, cycles after the second were characterized by a progression only to stage 2 which persisted until the next eye movement period and stage 1. However, this was partly an artifact of the EEG categoriza-

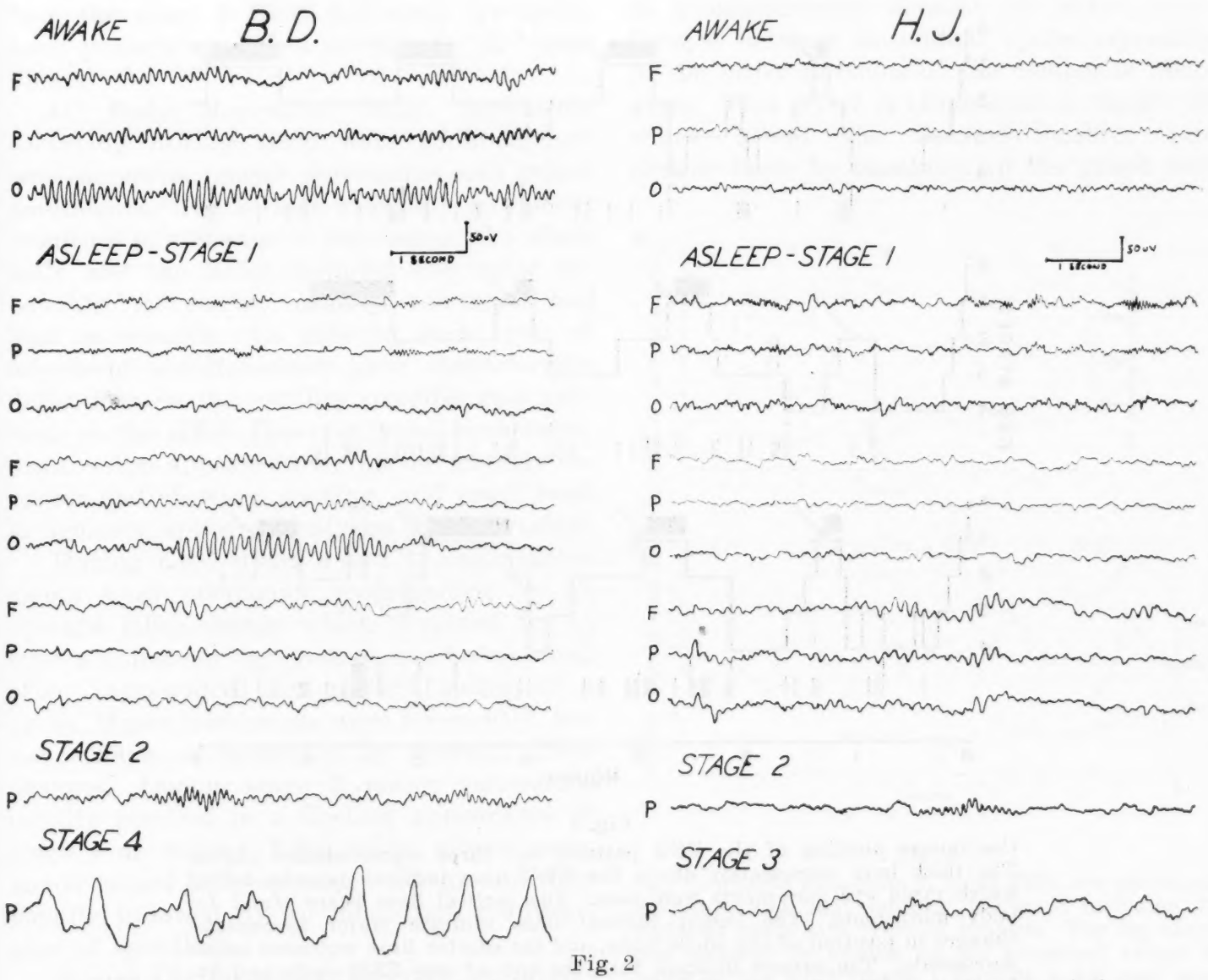


Fig. 2

EEG samples from two subjects to illustrate the classification of patterns and some of the variations in the stage 1 category associated with rapid eye movements. In the waking and stage 1 samples, each group of three tracings, F — frontal, P — parietal, O — occipital, is simultaneous. All samples were taken from one night's recordings.

tion since even in these cases there was obviously a progression to a "deeper" stage 2 and then a change to a "lighter" stage 2 before the onset of stage 1. There were, of course, many irregularities in the smooth sequence of events just described. Upward changes in the EEG often occurred in the middle of the cycles concomitant with body movement only to settle back to the previous level.

Occasionally, when the upward change of the first cycle occurred, it reached a very light stage 2 which persisted for many minutes *without* giving way to stage 1 and rapid eye movements and then deepened again to stage 3 or 4. When this happened, the middle of the period of the stage 2 EEG was considered to be the end of the first cycle with the interpretation that the mechanism usually inducing the upward change to stage 1 was not active enough to get beyond stage 2. This occurred about 20 per cent of the time in this series of experiments. Eye movements never failed to appear, however, toward the end of the second cycle. Figure 3 shows examples of the EEG plotted continuously in several subjects for a night's sleep. Successive beginnings of what have been designated cycles are indicated by arrows. Eye movements are represented by thick bars and body movements by vertical lines. In this type of plotting gradual change through a continuum cannot be shown. When the EEG was judged to have reached a different stage an abrupt change was made on the graph.

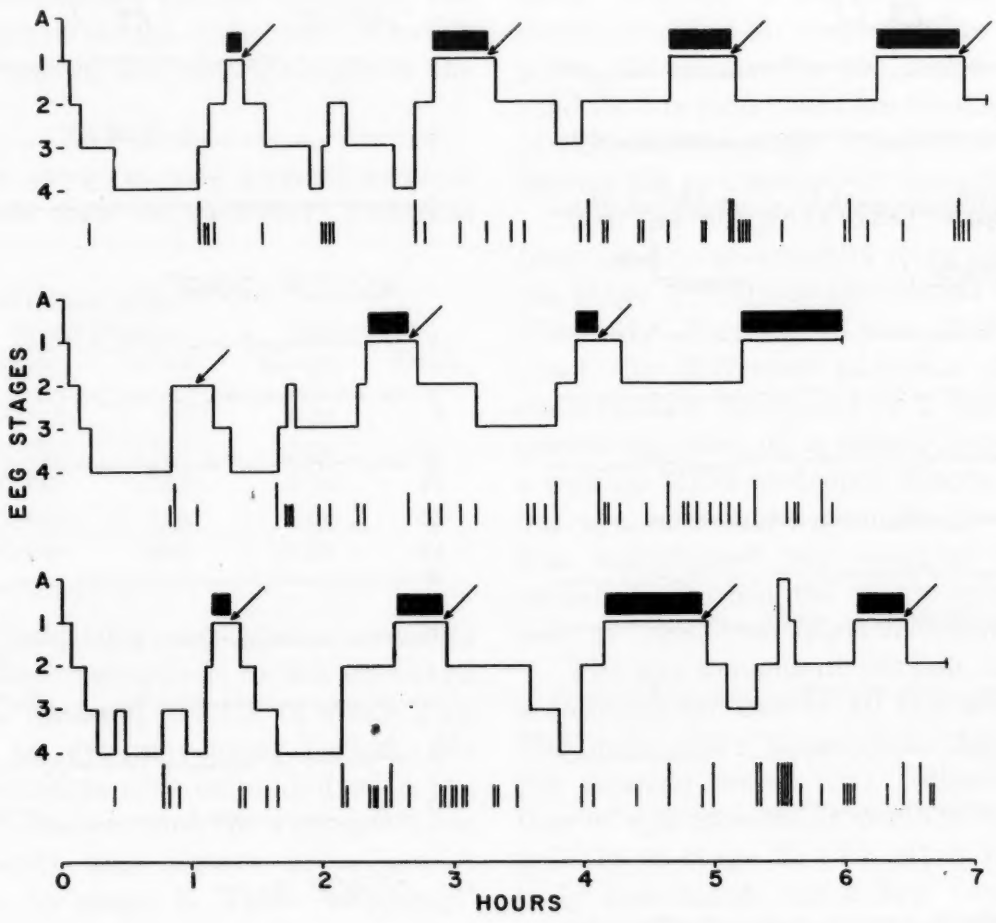


Fig. 3

Continuous plotting of the EEG patterns for three representative nights. The thick bars immediately above the EEG lines indicate periods during which rapid eye movements were seen. The vertical lines below stand for body movements. The longer vertical lines indicate major movements, changes in position of the whole body, and the shorter lines represent minor movements. The arrows indicate both the end of one EEG cycle and the beginning of the next.

The distribution of the occurrence of

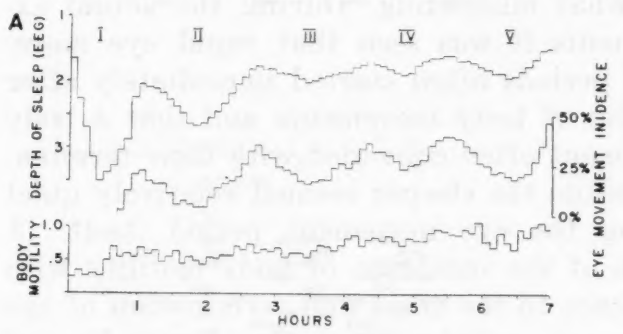
spontaneous "K" complexes showed interesting peculiarities. As has been observed by others (Davis *et al.* 1939), this wave form appeared most frequently during periods of a low voltage spindling EEG. However, it was generally of greater amplitude and more frequent during the stage 2 EEG preceeding an eye movement period than following. In fact, the stage 2 EEG following eye movement periods was often devoid of "K" complexes.

C. *Body Movement.* Body movements occurring during sleep were grouped into two categories, major movements and minor movements. The former were any movement resulting in a change in position of the whole body and the latter included any other detectable movement, usually stirrings and limb movements. In general, each type of movement simultaneously gave characteristic deflections on the motility recorder and artifacts on the EEG. However, small limb movements often appeared only on the motility recorder and chewing, sucking, and small head movements appeared only as EEG artifact.

During EEG stages 3 and 4, major movements were invariably accompanied by an upward EEG change which persisted for at least a minute or two and, as has been stated, often represented the upward swing of a cycle. Minor movements were frequently, but not always, accompanied by upward EEG changes. During stage 2, major movements usually resulted in a fleeting appearance of stage 1 or waking EEG while minor movements caused little apparent change and were usually followed by an immediate reappearance of spindling.

Figure 4A illustrates the cyclic variations in EEG, incidence of rapid eye movements, and incidence of body motility and their interrelations. The EEG stages, incidence of rapid eye movements and body motility during each successive 6 min. period after the onset of sleep were added and averaged for all 71 nights. Even without complete control over certain factors that might have disturbed the sleep pattern, such as the chance occurrence of excessive noise outside the building, and environmental temperature and humidity changes, a clearcut, regular, cyclic variation in EEG and eye movements was seen for the group with the peaks of eye movement related to the peaks of the EEG cycle. A concomitant variation in body motility is suggested.

Since the cycle lengths tended to vary with the subject, the lining up of all the nights in terms of the sleep onset resulted in a considerable amount of phase interference between individual cycles especially in the latter portions of the composite histogram. This effect is eliminated in figure 4B which brings the interrelationships into clearer focus by breaking up the graph into



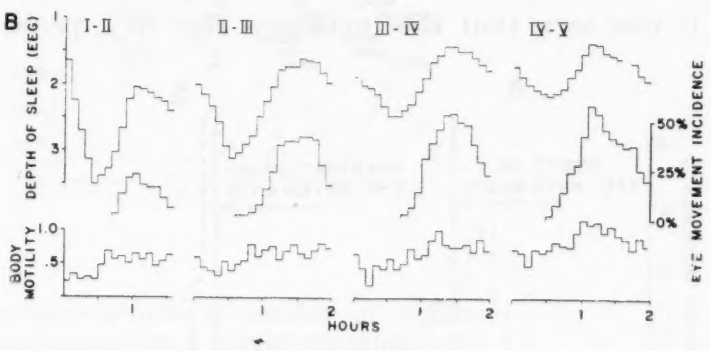


Fig. 4

(A) Composite histogram of mean EEG, eye movement incidence, and body motility incidence including 71 nights of sleep data from 33 subjects. The top curve was obtained by adding up the numerical values in terms of the EEG stages 1 through 4 for each successive 6 min. interval after the onset of sleep and dividing by 71. In the middle curve, the numbers of minutes of eye movement in each successive 6 min. interval were added for the 71 nights. If every night had showed 6 full minutes of eye movement in the same interval, a 100 per cent incidence would have been attained. The third curve is average incidence of body movement in arbitrary units. A major movement equalled 2 units and a minor movement, 1.

(B) This graph is the same as A except that the 6 min. intervals are oriented in terms of the beginnings of successive cycles instead of the initial sleep onset. This reduces the effect of temporal dispersion and further shows that there are no eye movements for a considerable time after the beginning of a new cycle.

individual cycles, that is, placing the beginnings of all subsequent cycles at the same place so that the start of the graph of the 2nd cycle contains the beginnings of all the individual 2nd cycles regardless of where they occurred in relation to the initial onset of sleep and likewise for the 3rd and 4th cycles. In addition to a more sharply defined EEG-eye movement relationship, it now can be clearly seen that the incidence of gross body motility also undergoes a cyclic variation.

The fact that the mean incidence of gross body movement seems to rise to a peak concomitant with the EEG peak in figure 4B is somewhat misleading. During the actual experiments it was seen that rapid eye movement periods often started immediately after a series of body movements and that a body movement often coincided with their termination while the sleeper seemed relatively quiet during the eye movement period itself. A graph of the incidence of body motility with reference to the onset and termination of eye movement periods was made (figure 5) and it was seen that the incidence rose to a peak, dropped sharply at the onset of eye movements, and rebounded abruptly as the ocular activity ceased.

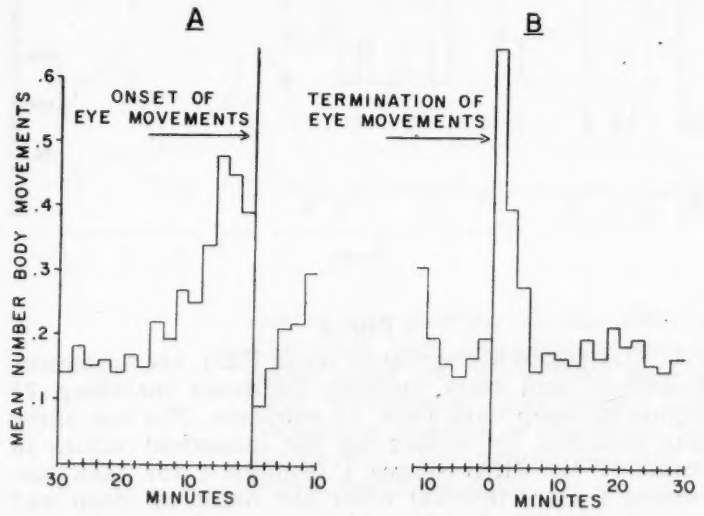


Fig. 5

A composite histogram of the incidence of body movement in terms of the onset and termination of rapid eye movement periods. It brings into clear focus the tendency of body movement to increase up to the beginning of eye movements at which point it decreases sharply and rebounds at the end of the period of eye activity. Since the eye movement periods were of widely varying lengths, two separate histograms were necessary. Data from 198 eye movement periods is included. Remembering that eye movements and stage 1 EEG were concomitant, the graph also indicates that more body movements occurred while a stage 2 EEG was present than a stage 1.

On seven nights, the experimenter sat near the bed and watched the subjects throughout the entire night with the aid of a dim light, making notations of the occurrence and quality of the body movements and their duration. These observations confirmed what has been stated, but in addition, it was noticed that during rapid eye movement periods numerous very small distal limb and digital movements occurred which did not register on either the EEG as artifacts or the motility recorder as deflections. Thus, although gross body and limb movements were decreased during rapid eye movement periods, there seemed to be a unique increase in very fine movements which were almost entirely absent during the interspersed periods of ocular quiescence.

II. Stage 1 EEG without eye movements.

It was mentioned previously that no rapid eye movements were seen during the onset of sleep when the EEG passed through stage 1 in going from the patterns of full wakefulness to the spindle and delta stages, although this stage 1 EEG seemed to be identical with those occurring later in the night concomitant with actual eye movements. Since the later stage 1 patterns are apparently associated with dreaming (Dement and Kleitman 1957), it seemed desirable to investigate the stage 1 EEG at the sleep onset with regard to dream activity in spite of the lack of rapid eye movements.

Ten subjects were awakened a total of 50 times by a buzzer while the EEG showed patterns within the range encompassed by the category, stage 1, during the initial onset of sleep and in addition, were occasionally awakened during rapid eye movement periods later in the night. They were asked to give their impressions of what had been in their minds before the awakenings and, if possible, to differentiate between the state of mind preceding the early versus the later awakenings.

In all cases, the subjects felt that, although the mental content during the onset of sleep

was often "dream-like", it was distinctly different from an actual dream. They invariably stated that they were not asleep and that the mental imagery was not as organized or "real" as that occurring in dreams. A variety of images and sensations were described that might be called hypnagogic, such as "floating", "drifting", "flashing lights", etc. The later eye movement, stage 1, awakenings generally elicited dream recall and the impression of having been "really asleep".

A further test of the difference between the two phases was done by examining the auditory thresholds necessary to elicit a response from the subjects. The stimulus was a 1000 cycle tone sounded for 10 sec. and the response was clenching the jaw 3 times which gave easily identified muscle potentials in the EEG record. If no response was obtained, the intensity was raised slightly and the stimulus was repeated after one minute had elapsed. This procedure was continued until the subject responded. Intensity was calibrated in terms of voltage across the loudspeaker.

A total of 32 responses was obtained from the 10 subjects during the stage 1 EEG at the onset of sleep and 26 responses were elicited during the stage 1 EEG periods accompanying eye movements later in the night. The threshold ranged from 0.1-0.4 V. at the sleep onset and 1.0-1.8 for the later awakenings. The difference of the means was significant at the $p<.001$ level. Further attesting to the significance of this difference was the fact that the stage 1 EEG at the sleep onset was always allowed to progress to a complete disappearance of alpha rhythm while the

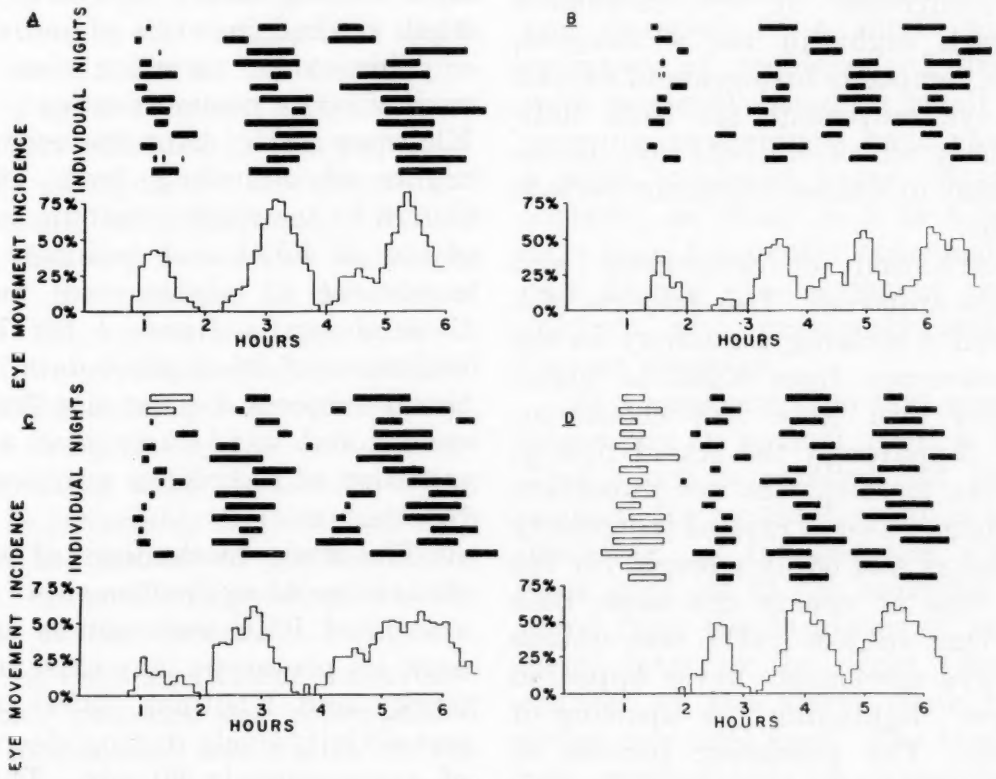


Fig. 6

The regularity of rapid eye movement periods over a number of nights in 4 individual subjects (A-D). Each bar represents a single eye movement period and each horizontal line of bars, a single night. The open bars in C and D stand for periods of stage 2 EEG which represent the peak of the first sleep cycle. Composite histograms of eye movement incidence for each individual are placed below the group of nights to which they refer. In general, these histograms show the cyclic variation more clearly than figure 4 A, i.e. individuals seem to be more regular than the group as a whole.

EEG at the time of the stimulus during rapid eye movement periods often contained considerable amounts of alpha activity.

III. Individual differences in normal sleep.

Four subjects were further studied for from 12 to 16 nights per subject in a third group of experiments to obtain some information regarding individual differences.

Figure 6, A-D, shows the durations and patterns of occurrence of eye movement periods for each night in the 4 subjects, together with a composite histogram of overall incidence of eye movement for each individual. The bars which indicate eye movement periods also, of course, represent periods of stage 1 EEG.

Certain individual characteristics and differences were apparent. Two subjects (6A and 6D) showed a striking regularity in the pattern of occurrence from night to night, while the other two were less consistent, especially 6C. Apparently the actual time at which they went to sleep was not important since for the former two it ranged irregularly over about 3 hours and oddly enough, for the latter two it was at nearly the same time every night. One subject (6D) was unique in that rapid eye movements never appeared during the first ''lightening'' or upswing of the EEG cycle. The persisting periods of stage 2 representing the first peak in this subject are indicated by open bars. The average cycle lengths varied somewhat, being longest in 6A and shortest in 6D. The subject illustrated in 6C seemed to have short cycles in the first half of the night and long ones in the second half, but this may have been at least partially an artifact of his irregularity. The average duration of eye movement periods was greatest in 6A and least in 6B. In general, it appeared that individual subjects were somewhat more regular than the group as a whole.

DISCUSSION

Regularly occurring periods of rapid, conjugate eye movements were recorded without exception during each of 126 nights of undisturbed sleep. The periods of eye movements were invariably concomitant with a characteristic EEG pattern, stage 1, while the interspersed periods of ocular quiescence always showed ''deeper'' patterns, stages 2, 3, and 4. The same results were obtained in an additionel 20 nights during which sleep was interrupted for the determination of auditory threshold and the presence of dream recall. The composite EEG for 71 nights from 33 subjects showed a regular cyclic variation with a period of about 90-100 min. and the regularity was even more striking when studied in terms of individual subjects.

This cyclic variation was reported in a preliminary communication (Dement and Kleitman 1955) after the accumulation of 43 nights of recording from 16 subjects. It should be mentioned that the composite histograms of EEG and incidence of eye movements for 43 nights were quite similar to those shown in figure 4 for 71 nights. The inclusion of 28 nights' data from 17 additional subjects did not significantly alter the curves and it is likely that a further accumulation of recordings would add little to the results.

The basic mechanism of such a regular occurrence of eye movements (dreaming) and associated EEG variation is unknown. However, its prototype may exist in infants (Aserinsky and Kleitman 1955) as an observed rest-activity cycle during sleep with a period of approximately 60 min. The greater cycle length seen in adults resembles the lengthening of other physiological cycles, i.e. cardiac and respiratory, and may be related to their lower basal metabolic rate. In any case, the regularity and apparent universality of this sleep cycle in adults indicate that it is an intrinsic part of the sleep pattern rather than a result of external disturbance.

A close perusal of the all-night EEG graphs published by Loomis *et al.* (1937), Knott *et al.* (1939), and Díaz-Guerrero *et al.* (1946) reveals a tendency toward this type of cyclic variation. Henry (1941) found that 20 per cent of the EEG during a night's sleep was occupied by a low voltage pattern which is almost identical with the percentage of stage 1 found in this study. It seems possible that sampling techniques rather than continuous recording, miscategorization of the

EEG due to eye movement potentials appearing in brain wave leads, and disturbances of the subjects may have been responsible for these authors not noting the marked regularity described here. Long periods of low voltage EEG called "null" by Blake and Gerard (1937) and "early morning sleep" by Gibbs (1950) probably represent the lengthy rapid eye movement periods often occurring toward the end of the sleep period. It is also gratifying to note that Brooks *et al.* (1956) have recently published graphs of the mean EEG showing cyclic variations in depth of sleep that are similar to the results previously reported by us (Dement and Kleitman 1955) and further extended in this paper.

In the study of rapid eye movements and dreaming (Dement and Kleitman 1957) it was suggested that eye movements should be the criterion of the presence or absence of dreaming and they were used as such in this study. However, it should be pointed out that the EEG is actually a better criterion. Thus, *with the exception of the initial onset of sleep,* a persisting stage 1, non-spindling EEG seems to be invariably concomitant with dreaming while the amount of eye movement may be large or small depending on the actual imagery of the dream.

As stated, the only significant occurrence of stage 1 EEG patterns not accompanied by rapid eye movements was found at the onset of sleep. However, the auditory thresholds were still quite low at these times, and awakenings elicited descriptions of what may be called hypnagogic reveries and the feeling of being still awake. On the other hand, the stage 1 periods later in the night were invariably associated with eye movements, raised auditory thresholds, dream recall, and the feeling of having been "really asleep". The difference probably has to do in part with a persisting awareness of being awake in the former case, whereas the dream periods generally followed an interval of deeper sleep and thus the sleepers had no such cue to tell them the dream hallucinations were not real. They therefore behaved as though they were real, at least to the extent of executing appropriate eye movements. The raised auditory thresholds may have meant either that the subjects were too engrossed in the dream content to notice outside stimuli, or an actual difference in auditory excitability.

The incidence of stage 1 EEG patterns and rapid eye movements during undisturbed all night sleep and the quantity of dream recall obtained by awakening subjects during these periods (Dement and Kleitman 1957) suggests the normal occurrence of a much greater amount of dreaming than was heretofore realized, both in the invariability of its presence from night to night and in its frequency and duration in a single night. Previous estimates of incidence of dreaming, which were generally based on recall obtained after morning awakenings, have varied from once a night to almost never (Ramsey 1953). In contrast, as many as 5 or 6 lengthy dreams have been frequently described after awakenings during eye movement periods even by subjects who previously stated that they "never dreamed".

It is apparent then that most of the dream experience in normal sleep is never recalled. That which is recalled can probably be accounted for by the fortuitous interruption of dreaming, as for instance when the alarm clock goes off in the morning. It should be noted from the incidence of rapid eye movements later in the night (fig. 4) that the chances of the alarm clock interrupting a dream are very good. The level of consciousness represented by dreaming would thus seem to be associated with a very short memory span, perhaps in some way analogous to that seen in very young children and in old people, who often have difficulty in recalling recent events. In some instances, even when the dream content was reported clearly and coherently after an awakening during an eye movement period, a re-description in the morning was fragmentary and distorted.

Several points of interest are seen when the results of the earlier study where subjects were awakened to elicit dream recall (Dement and Kleitman 1957) are compared to the results of this study on uninterrupted sleep. In the earlier study, subjects were awakened an average of 6 times a night or about once an hour. The main effect of these

awakenings was a more frequent occurrence of eye movement periods. This was clearly seen in one subject who served in both the earlier study and this one. As illustrated in figure 6A, he showed an average of about one eye movement period every 110 min. When his sleep was interrupted, he averaged one eye movement period every 70 min. over 11 nights. This reduction in cycle length seemed to be due to the artificial termination of the eye movement periods by an awakening when their duration was much less than their average in undisturbed sleep.

As a rule, eye movements did not immediately recur upon the return to sleep. In 191 awakenings during eye movement periods in the earlier study, there were only 16 instances of recurrence. Interestingly enough, 12 of the 16 were preceded by 1-5 min. of stage 2 sleep without eye movements, and 9 of the 16 were occasions when the subjects were unable to remember dreams and thus only had to say, "I don't remember", before going back to sleep. Furthermore, it was noted in the part of this study concerning auditory thresholds, where the subjects had only to clench their jaws three times, that eye movements recurred much more often, about 50 per cent of the time. It seemed that when the subjects had to awaken fully and describe a dream, the return to sleep generally was more like the initial sleep onset and a new cycle was initiated, whereas a brief or "partial" awakening often allowed the eye movements to continue. Awakenings during the interspersed periods of ocular quiescence seemed to have little effect, in that eye movements neither started on the return to sleep nor was the time of onset of the next eye movement period markedly changed from what would have been expected in the absence of an awakening. One explanation for this minimal effect could be that ocular quiescence was concomitant with deeper sleep (EEG stages 2, 3, and 4) and since the inability to recall dreams meant a relatively short period of wakefulness, the subjects were able to return to the deeper levels of sleep without disturbing the cycle pattern.

The deepest sleep in terms of EEG patterns was usually seen in the first hour and nearly all the high voltage delta activity occurred in the first three hours. This parallels depth of sleep curves in terms of eye movement incidence, auditory arousal threshold (Blake and Gerard 1937), and in a general way, body motility, but not curves in terms of heart rate, skin resistence, and body temperature (Kleitman 1939). Also, body motility incidence did not consistently parallel the brain wave patterns in this study. Although it was lowest during stage 4, more movements were actually initiated in the presence of stage 2 patterns than during stage 1. Depth of sleep would seem to be a rather elusive characteristic which differs according to the specific variable used to describe it.

EEG and Consciousness. One of the most intriguing properties of the electroencephalogram has been the close correlation of some of its characteristic patterns with certain functional states of the organism. It has always been hoped that clarification of the mechanisms producing these patterns would yield insight into the neural basis of the functional states with which they are associated. An example in which these hopes have been at least partially realized can be seen in recent work on the brain stem activating system. Since stimulation of the reticular formation was found to elicit an EEG pattern associated with the waking state, while its ablation gave patterns generally associated with somnolence, the system was said to function in maintaining wakefulness. Without the correlation of EEG pattern and functional state, such a conclusion could not have been made.

One would like to use the EEG in a similar way to aid in defining the neural basis of consciousness. Of course, this immediately presents the very difficult problem of formulating an adequate definition of "consciousness". In the past, this obstacle has often been side-stepped by equating consciousness with wakefulness and unconsciousness with sleep. In addition to avoiding semantic entanglement, this device would seem to afford the advantage of conveniently relating levels of consciousness at least grossly to brain wave patterns. However, such a definition is in reality of little value because it tends to result in mere repetitious dis-

cussion of what is known about the neural basis of wakefulness, substituting for it the word ''consciousness''.

It should be noted that sleep and wakefulness, as states, can be objectively observed and to some extent measured. They can be compared and contrasted, and they can usually be distinguished from each other by simple inspection. In consciousness, on the other hand, the sleep-wakefulness dichotomy is absent. There is only one state whose criteria are mainly subjective, though partly objective, as the observer is able to make some inferences. One may omit the use of the term unconsciousness and merely refer to levels of consciousness varying from zero to a high level, depending upon the communications and performance of the individual.

Even with a very simple description of consciousness, i.e. the ability to analyze, integrate, and subsequently recall experience, it is obvious that a high level of consciousness is not always limited to wakefulness, nor does sleep always imply a very low or zero level of consciousness.

New-born infants, anencephalous children, and decorticate dogs or cats may exhibit wakefulness, but their level of consciousness is close to, if not at, zero. In delirium, fugues, icteral or post-icteral automatism of psychomotor epilepsy, a person may be judged to be behaviorally awake, but his level of consciousness is very low.

Of course, the above examples are special cases, but the converse, consciousness during frank sleep as represented by the level of analysis, integration, visual imagery, and subsequent recall seen during dreaming, is virtually universal and quite normal. Since dreaming in the past was said to occur during all the EEG levels of sleep, one had to conclude that at least in sleep there was no particular relation between brain wave patterns and consciousness, and that the neural functioning, whatever it might be, underlying the production of spindles and high voltage slow waves, as well as low voltage patterns, was compatible with this degree of mental activity.

That this lack of relation between brain waves and consciousness, as represented by dreaming, is not the true picture seems clearly indicated by this study. It was seen that the rapid eye movements during sleep, which almost certainly are concomitant with dreaming, occurred when, and only when, the EEG was ''above'' the spindling stage — that they were uniquely associated with a stage 1 EEG. Consequently, whatever its level during dreaming, consciousness ceases or at least falls below this level, in the normal course of events, when spindling appears in the EEG.

The hypnagogic reveries in falling asleep also apparently cease when the EEG reaches the spindling stage. Davis *et al.* (1938), in several hundred awakenings, elicited all sorts of reports of images and sensations from subjects whose EEG patterns had not progressed beyond their ''B'' stage, but when the ''C'' stage (spindling) appeared, awakenings no longer elicited hypnagogic recall and subjects said they were ''really asleep''. These findings were confirmed in this study.

With dreaming and hypnagogic reverie assigned to a definite EEG stage, there exists at least a fairly consistent relation between the EEG and levels of consciousness and it becomes possible to undertake the second step of considering the neural origin of these patterns as representing the basis of consciousness itself.

An examination of the mechanism of spindling would seem to be the most fruitful point of departure. In the first place, the appearance of sleep spindles represents a rather sharp, all-or-nothing type of brain wave change. They are either present with a wide distribution and a characteristic frequency and wave form (although there are topographical differences in frequency) or they are not seen at all. Secondly, their appearance or disappearance appears to be associated with a sharp change in the level of consciousness.

Although no completely satisfactory explanation has been extended for the mechanism of sleep spindles, it seems to be generally agreed that the integrity of certain subcortical structures is necessary. Spindling was found to be suppressed in humans after subcortical vascular accidents (Cress and Gibbs 1948) and prefrontal lobotomy

(Lennox and Coolidge 1949, Krueger and Wayne 1952), and in a patient with thalamic syndrome (Henriksen, Grossman and Merlis 1949). Subcortical lesions in cats (Knott and Ingram 1951) also seem to disrupt the appearance of spindle patterns. If barbiturate bursts and recruiting responses are considered analogous to normal sleep spindles rather than alpha rhythm, as is suggested by Ralston and Ajmone-Marsan (1956), then the role of the thalamus becomes very compelling.

It should be pointed out that even though the spindles may represent the synchronous activity and influence on the cortex of a diffuse thalamo-cortical system, disturbance of the pattern does not necessarily imply that the system has been totally destroyed nor that it is completely functionally incapacitated. That several similar systems exist together, in humans at least, was indicated by Lennox and Coolidge (1949) who found that prefrontal lobotomy with probable subsequent degeneration of nucleus centralis medialis of the thalamus only affected the frontal 12/sec. spindles and left 14/sec. spindles unimpaired in both parietal and frontal regions. Thus, although the spindle patterns might be disturbed, it would probably take far larger lesions to totally destroy the systems that produce them, and such lesions would probably be incompatible with consciousness.

Some sort of diffuse diencephalic-cortical integrating system has been hypothesized by Penfield (1938, 1952) as a necessary component of conscious activity. If the synchronous patterns of spindling may be said to represent functional inactivity in such a system, assuming that during mental processes neural activity is essentially random, then the relation of the spindle patterns to consciousness becomes neurologically meaningful. That the waking EEG lacks spindles and is usually correlated with a high level of consciousness is well established. The results in this paper indicate that all periods of non-spindling EEG during sleep are also correlated with consciousness either as dreaming or hypnagogic reveries. The appearance of spindling signals a drop in the level of consciousness and is concomitant with functional inactivity (i.e. synchronicity) of a diffuse subcortical-cortical integrating system.

The mere appearance of synchronous waves in the cortex by itself, however, certainly does not necessarily mean functional inactivity. A synchronous, persistent alpha rhythm may be present during very complex mental activities. The waves at the cortex more probably represent variations in membrane potentials, possibly in the dendritic layers, rather than synchronicity of actual nerve impulses. However, if the waves are due to subcortical influences, then there is almost certainly a synchronicity in nerve impulses ascending to the cortex. Thus, the presence of regular variations in cortical potential, as in alpha rhythm, may influence but not necessarily hamper the random flow of nerve impulses during thinking, whereas synchronous barrages of nerve impulses in diffuse projection systems might mean that the neural elements are unavailable for the essentially random firing of high level integration. It might be added that since there is no evidence of any consciousness during the deepest stages of sleep characterized by predominance of 1-2 sec., high voltage waves, the relative lack of spindling at this time is more likely a further depression of these systems rather than their activation.

The brain stem activating system is also very probably involved in producing the periods of rapid eye movement. Certainly the stage 1, low voltage EEG seen during these periods is at least partially "activated". The regions of the brain stem that produce activation of the EEG in animals apparently include both the bulbar ventromedial inhibitory (Moruzzi and Magoun 1949) and facilatory (French, von Amerongen and Magoun 1952) reticular areas of Rhines and Magoun (1946) and Magoun and Rhines (1946). In this study, it was seen that the incidence of gross body movement was decreased during rapid eye movement periods. This may mean that mainly the inhibitory area was active at these times. A teleological basis might be that the dreamer is fixed or arrested by his preoccupation in the dream picture, analogous to the way one is held in motionless fascination by an exciting movie. Of course, it does

not account for the objective stillness of the dreamer when he is executing some violent movement in the dream, such as running, fighting, etc.

It appears to be possible in certain cases to produce a dissociation between the EEG and objective behavior. Wikler (1952) found after injection of atropine in dogs that the animals "were definitely 'excited' and had to be restrained to permit recording, at a time when the 'sleep patterns' were evident in the EEG tracing", and Rinaldi and Himwich (1955) saw stable sleep patterns in curarized, atropinized rabbits even during apparent behavioral arousal. There is also one report in the literature (Hamoen 1954) of sleep patterns including spindles occurring in 6 behaviorally awake humans suffering from narcolepsy, epilepsy, trauma, and schizophrenia.

On the other hand, patterns very nearly resembling those generally associated with full wakefulness, called "drowsy" patterns by Gibbs (1950), "transitional" by Simon and Emmons (1956), and "stage 1" in this paper, are seen at the onset of sleep, and also during the frank behavioral sleep with raised auditory threshold associated with dreaming. In addition, EEG patterns virtually indistinguishable from waking patterns have been observed to occur periodically in tracings taken in this laboratory from cats during a lengthy interval of normal, unsedated sleep.

Thus, as has been pointed out, conciousness may vary independently of sleep-wakefulness behavior, and likewise, EEG patterns may be in some cases dissociated from behavioral sleep and wakefulness. A consistent parallelism between levels of conciousness and EEG patterns is difficult to establish but may exist. In at least three qualitatively similar mental states, the EEG appears to be identical. One, dreaming, is seen during frank behavioral sleep. Another is represented by the hypnagogic reveries occurring in the transition between sleep and wakefulness. The third is from the very interesting McGill "boredom" studies (Heron 1957) where subjects showed the appearance of minimal slow wave activity and a slight decrease in the frequency spectrum of alpha rhythm while awake but mentally disorganized and actively hallucinating. These EEG changes would seem to resemble those described in this paper as characteristically associated with dreaming. An even lower level of consciousness probably existed in the wakeful, atropinized animals showing sleep EEG patterns. In view of these considerations, it would appear that behavioral criteria should take precedence in determining the presence of sleep or wakefulness, whereas the electroencephalogram may be more closely related to levels of consciousness.

SUMMARY

In 33 adults, discrete periods of rapid eye movement potentials were recorded without exception during each of 126 nights of undisturbed sleep. These periods were invariably concomitant with a characteristic EEG pattern, stage 1.

Composite histograms revealed that the mean EEG, eye movement incidence, and body movement incidence underwent regular cyclic variations throughout the night with the peaks of eye and body movement coinciding with the lightest phase of the EEG cycles. A further analysis indicated that body movement, after rising to a peak, dropped sharply at the onset of rapid eye movements and rebounded abruptly as the eye movements ceased.

Records from a large number of nights in single individuals indicated that some could maintain a very striking regularity in their sleep pattern from night to night.

The stage 1 EEG at the onset of sleep was never associated with rapid eye movements and was also characterized by a lower auditory threshold than the later periods of stage 1. No dreams were recalled after awakenings during the sleep onset stage 1, only hypnagogic reveries.

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SOME OBSERVATIONS ON LAMBDA WAVES AND PERIPHERAL STIMULATION

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INTRODUCTION

Lambda waves were first reported by Evans in 1949 (1952, 1953). He found that the waves were enhanced by pattern vision and disappeared on eye fixation. They were also described by H. and Y. Gastaut (Y. Gastaut 1951; Gastaut *et al.* 1951), and the findings verified by Cobb and Pampiglione (1952). Roth and Green (1953) described lambda waves as a normal physiological phenomenon, which was not necessarily associated with any particular pathological condition, as had been previously suggested, but was enhanced when the eyes were making scanning movements over a patterned field. Also, some waves with the same shape and location as the lambda waves were found during a certain stage of sleep, usually at about the same stage that K-complexes could best be evoked: in deeper sleep these waves disappeared. This observation is mentioned in a recent paper on the K-complex (Roth, Shaw and Green 1956). Green (1954) reported on lambda waves in relation to some visual tasks from a series of experiments using only normal subjects. In the same year H. Gastaut and Bert (1954) described lambda waves that appeared in their subjects during the showing of cinema films. Rémond and Lesèvre (1956) have recently written about lambda waves in conjunction with picture tasks: these were seen using high gains and found in 61-99 per cent of their subjects. They mentioned that interest in the pictorial matter enhanced the appearance of these waves. Groethuysen and Bickford (1956) have made a study of lambda waves in various clinical conditions.

The first part of the study to be described here, undertaken in 1954, was made to try to elicit lambda waves by visual tasks with controlled and voluntary eye movements using normal subjects. The second part of the paper, which refers to a recent investigation, is an attempt to find out more about the origin of the waves by comparing their waveform and latency with respect to eye movement (which was found to be a necessary, though not sufficient precursor of the wave), with known responses to peripheral stimulation.

METHOD

The complete study was made on 94 normal subjects, mainly consisting of medical and hospital staff and friends who volunteered for 1-7 sessions lasting ½-2 hours each. The EEG was recorded in the conventional manner with the subject sitting comfortably in a well lighted room.

The technique of recording eye movements was that described by Bergman, Nathansen and Bender (1952). With this method, 2 channels were used for horizontal eye movements by placing electrodes in series from the right external canthus to the bridge of the nose, thence to the left external canthus, and arranged electrically, in our series, so that an eye movement to the left resulted in an upward pen deflection, and to the right in a downward deflection. Two channels were used for recording vertical eye movements with electrodes placed above and below each eye causing an upward pen deflection for looking up and a downward one on looking down (fig. 1). The example shows the EEG and the eye movements as recorded for 5 simple movements round a pattern of dots giving horizontal, vertical and oblique movements, together with the appearance of a blink. It should be noted that these eye movements do not affect the occipital recordings. Because conventional C.R. coupled amplifiers were used, the size of the deflection was dependent

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on the speed of the eye movement as well as on the width of the angle. In some of the earlier experiments, one channel recording obliquely across one eye was substituted for the 2 vertical eye movement channels, but in the more recent work, 2 channels recording horizontal and one channel recording vertical eye movements were used.

RESULTS

The findings in 1954 (Green 1954) may be briefly summarized as follows. Using data from 65 subjects, it was found that detailed pictures capable of arousing interest provided the best conditions for evoking lambda waves, so long as the recording gain was equivalent to at least 2 cm. for 50 μV., and the subject was

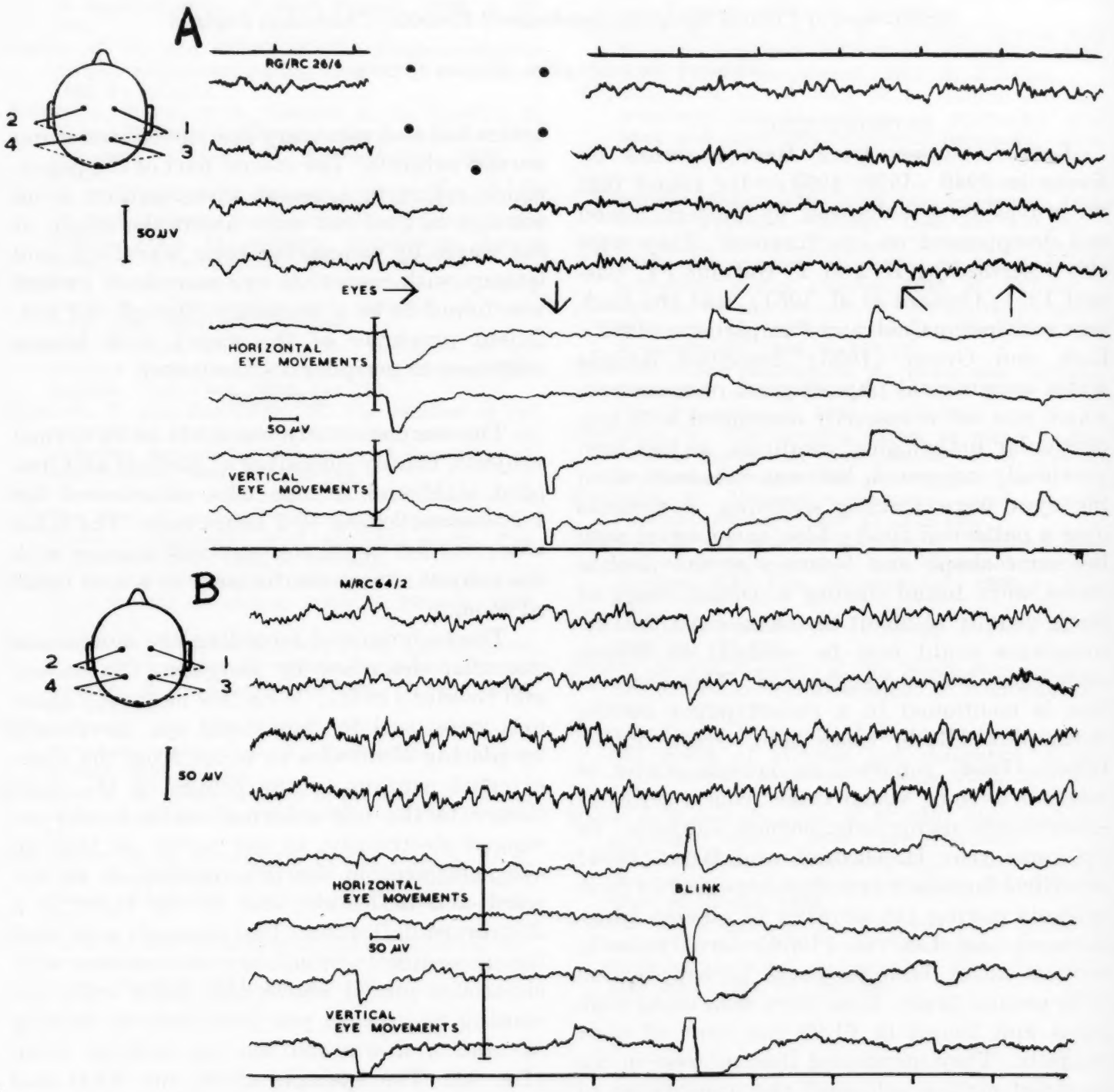

Fig. 1

Eye movement recordings. The arrows denote the direction of eye movements round a pattern of dots. The lower example shows the appearance of a blink.

sitting at ease in a reasonably good light. If the intensity of light was decreased, the amplitude of the waves also decreased, and they did not occur when the subject moved his eyes in darkness. Likewise, if the distance of the picture from the subject was increased or the image defocussed with the aid of glasses, the incidence and amplitude of the waves was lessened. The type of picture, be it line black-and-white, charcoal or coloured, did not influence the occurrence of the lambda waves provided that the person was sufficiently interested in the picture (fig. 2). A detailed picture enhanced the lambda waves very much more than reading. Rorschach cards, Matrices, Ishihara colour-blind tests, visuo-tactile tasks, jig-saw puzzles, after-image tests, reversing pictures and the like were not helpful in showing a consistent increase or decrease in the number of waves.

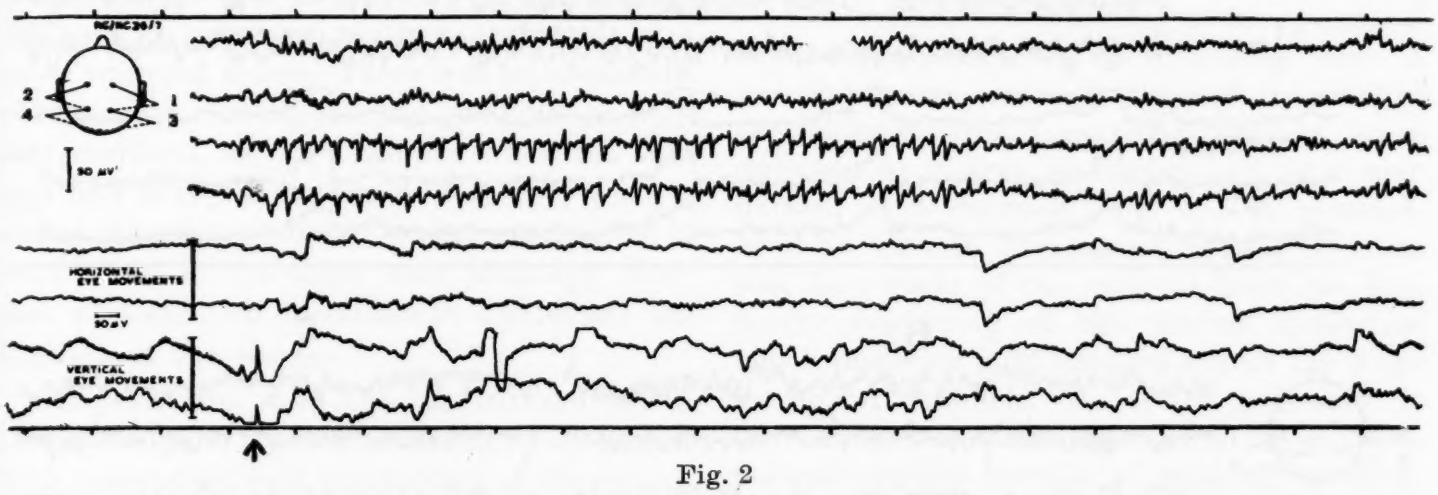

Fig. 2

Fading of lambda waves in a subject while looking at a picture he has seen about 12 times before. The subject commenced to look at the picture at the arrow. On the first occasion that he saw the picture, some four sessions previously, very good lambda waves appeared for 2 min.

Eye movement experiments included following the line of a pattern that represented the movements the eyes might make in looking at a picture, or having a sheet of numbers that were arranged in a design, the subject having to proceed from 1-20, looking for the next number and so completing the pattern in the same way as the line design, but having to find the next number with the directional aid of an arrow instead of following the line. Various scanning eye movements were carried out over striped and partly striped surfaces, with different widths of stripe.

An attempt was made to simplify the actual eye movements but at the same time to keep them under the voluntary control of the subject. This was done by making simple eye movements between 2 black spots on a white sheet, the subject looking first at one spot and then at the other, and then varying the distance between the spots; and secondly, altering the rate of movement of the eyes. This test was varied by using a number of spots so that different angles of eye movement were caused. The same eye movements were also carried out over a large, plain white sheet of paper.

Experiments were carried out in which the experimenter had control over the eye movements. Coarse and fine nystagmus movements were induced by a revolving drum that had vertical stripes in black and white painted on it, which was turned at various speeds and viewed directly or through a small window (fig. 3). The width of the stripes was varied, and sometimes the stripes appeared only on a section of the drum, the other part being plain white.

The above tests all appeared to inhibit the incidence of lambda waves. Eye fixation also caused the waves to disappear both with the head still and on moving the head while keeping the eyes fixed on one point, or following the arc of a small swinging object.

The question arose as to whether the waves could be caused by a system for the suppres-

sion of unwanted images to avoid the blurring of sight, an explanation recently suggested by Gastaut (1956). However, no difference could be detected in the record when the stripes of the drum were visible as such, the drum being turned at low speeds, or when they became blurred and the nystagmus movement failed to keep up, upon turning the drum at high speeds. The lambda wave activity in both cases was suppressed. There was also no difference in the occurrence of the lambda ments, such as following a pattern or searching for numbers, showed few lambda waves.

For the new study now to be described the numbers of normal subjects have been increased by another 29 people, but for a few calculations some of the records that were comparable from the previous series have been utilized for the present study. The numbers of subjects have therefore been given each time.

Using a sensitivity of 2 cm. for 50 μV., the subject was given a suitably detailed picture

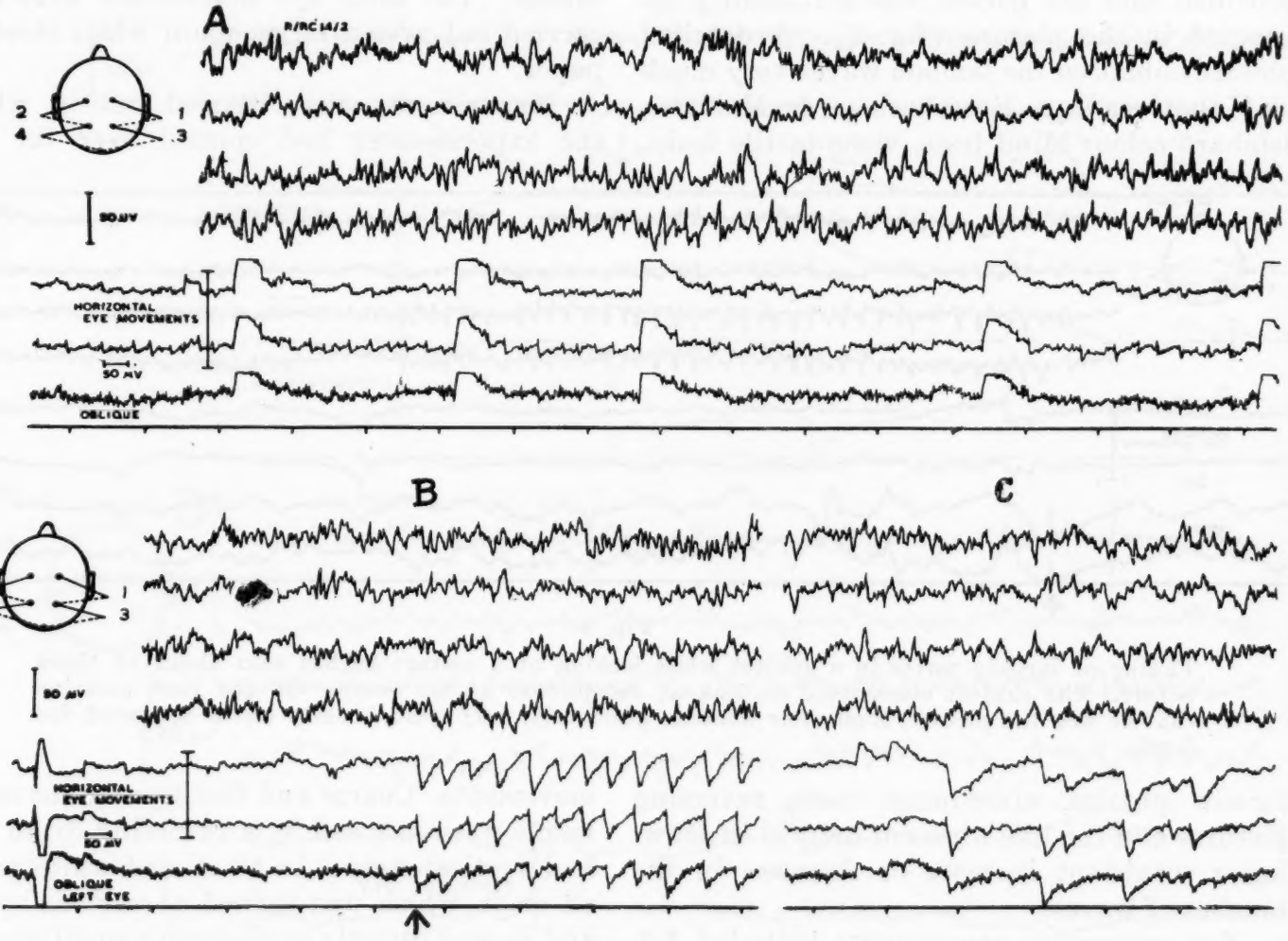

Fig. 3

A. The subject is reading.
B. The subject is facing a vertically striped drum. At the arrow, the drum is turned and a nystagmus movement caused.
C. The same drum is stationary and the subject making scanning eye movements across the stripes.

phenomenon when reading from letters that had varied spacing; the period of any waves remained within the same limits, whether the letters were widely spaced or close together, and reading did not enhance the waves nearly as much as looking at a picture. Furthermore, certain visual tasks that caused eye move- to look at. It was found that lambda waves were seen with varying clearness in all of the 42 normal subjects who did this test; 6 subjects showed the waves clearly with a lower gain. Of the 42 subjects, the lambda waves of 7 records were too poorly defined to be used for accurate measurement, chiefly be-

cause of masking by background activity. These records were discarded, but were counted in the overall totals: 8 more records, although used for measurements, were not very good. The resting EEGs showed an average selection of normal records with no marked trends as to type, using a normal working gain, but a detailed analysis was not undertaken.

Following the line of thought of the previous series, experiments were made in reading, through a mirror, writing and sketch copying, each test producing different types of eye movements. These tests did not produce a marked increase or decrease in the waves and most of the reading responses were difficult to measure as they appeared in a more rounded shape. There was no consistent change with reading silently or aloud, or with interruptions, as, for example, when the subject had to tap a rhythm at intervals when a sound stimulus occurred whilst continuing to read aloud at the same time, although there was at times, an inconsistent temporary inhibition of the waves.

Experiments were also carried out with a tachistoscope to try to evaluate any correlation with perception, and recognition of the object. Fast and slow exposures were used in this trial, the subject looking at the window in one test, and to the side of the box in another so that an eye movement was necessary with an alteration of focus when an object card was exposed. The cards shown had geometric drawings on them (e.g. a triangle with a line through it, a drawing of a watch face sometimes placed upside down, or words such as "colour photography" printed on 2 lines). To make quite sure of the degree of recognition as distinct from a guess, some of the words were altered or half inverted such as "flogale nightence", which nobody got right, or "albrega mathatemics" which 2 people did get right using comparatively long exposures. The length of the exposure was marked electrically. Few clear lambda waves were evoked from the background activity and these did not appear to correlate with any other factor or measurement.

Measurement of the Latency of Lambda Waves to Eye Movements.

Since looking at a picture appeared to provide the most favourable condition for eliciting lambda waves, the next problem was to try to see if there were any consistent relationship between spontaneous eye movement and the occurrence of lambda waves during this task. The method of eye recording was the same as that described above, using 3 eye movement channels, 2 recording the horizontal eye movement and one the vertical, with amplifier time constant 0.1 sec. and a sensitivity of 1 cm. for 50 μV. The sensitivity of the channels recording the EEG was 2 cm. for 50 μV. and the paper speed 61.5 mm. per sec.

The lambda wave latency to an eye movement was measured in the following way. A line was drawn vertically through the start of the clearest first occurring lambda wave irrespective of area, as determined by a comparison of 5 channels (fig. 4). A measurement to 0.1 mm. corresponding to 1.63 msec. was then made of the interval from the line, to the beginning of the nearest deflection which preceded it in time, in any of the 3 eye movement channels. It seemed necessary to have at least 5 channels covering the occipito-parietal regions because of masking by background activity. It was found that the majority of lambda waves were associated with eye movements of some sort. This was not observed in the experiments described in the previous paper (Green 1954) when a lower sensitivity for eye movements was used.

The average latency of all measurements of the lambda wave to an eye movement, involving 3,971 measurements, was 82 msec.: these included subjects with very good lambda waves and those with less clear but more common lambda waves. The average latencies for each individual subject (22 people) ranged from 67 to 85 msec., and the mean of these individual averages was 78 msec. The distribution for this population is thus seen to be non-symmetrical. The average latencies of the subjects with very good lambda waves tended to be slightly longer than for the subjects with ordinary lambda waves. It is of interest to see that the latency for the major

cortical response to a flash of light is considered to be between 70 and 88 msec. (Cobb and Morton 1952), and that a latency of 70 to 80 msec. for eye movement to lambda wave was reported by Gastaut (1956).

movements required by the task, was usually 97 to 130 msec. but these were not included because of the overloading of the amplifiers and also the difficulty in deciding which was really the last movement of the eye.

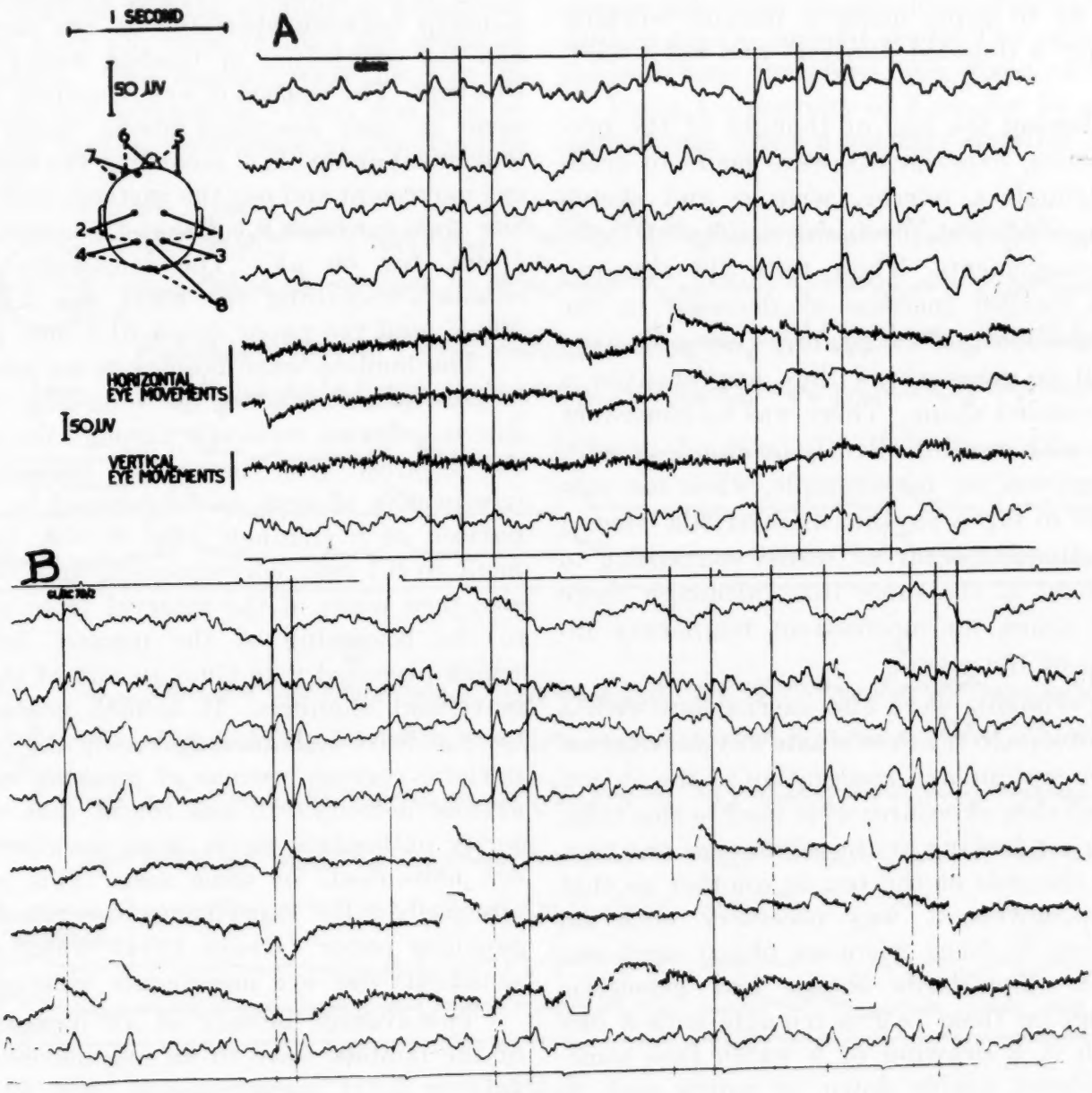

Fig. 4

The method of measuring lambda wave latencies; the measurements are taken to the nearest eye movement preceding the wave in time.
A. Shows parietal and occipital lambda waves.
B. Shows occipital lambda waves in another subject.

The range of the majority of latency measurements in a single record irrespective of type of picture varied within 16.3 msec. or 1 mm. measurement, either side of the average for the individual subject, but on isolated occasions rose to 2 mm. The latency of lambda waves to larger eye blinks as distinct from eye

Taken on different occasions, the individual latencies for each subject varied within 2 and 8 msec. of their own averages, the scores of the very good lambda wave subjects being the more consistent. This may have been largely due to a greater tendency for the less clear waves to be confused with back-

ground activity, as these records often showed the lambda wave area to be more scattered in the occipital and parietal regions and less synchronous.

The lambda waves varied in amplitude but their size did not individually correlate with the size or direction of eye movement, or to one sided preponderance of movement as recorded by this method. Examination of the form and distribution of the waves showed that often the predominent deflection was upwards, but at other times the main deflection was downwards and in some subjects this followed a hardly perceptible upward phase. Occasionally the downward occipital waves were phase reversed with similar waves in the parietal areas, but at other times they appeared independently of any other waves. It was found that measurements on the downgoing waves were more difficult to obtain and gave less consistent results, so that the calculations were made only on the upgoing waves.

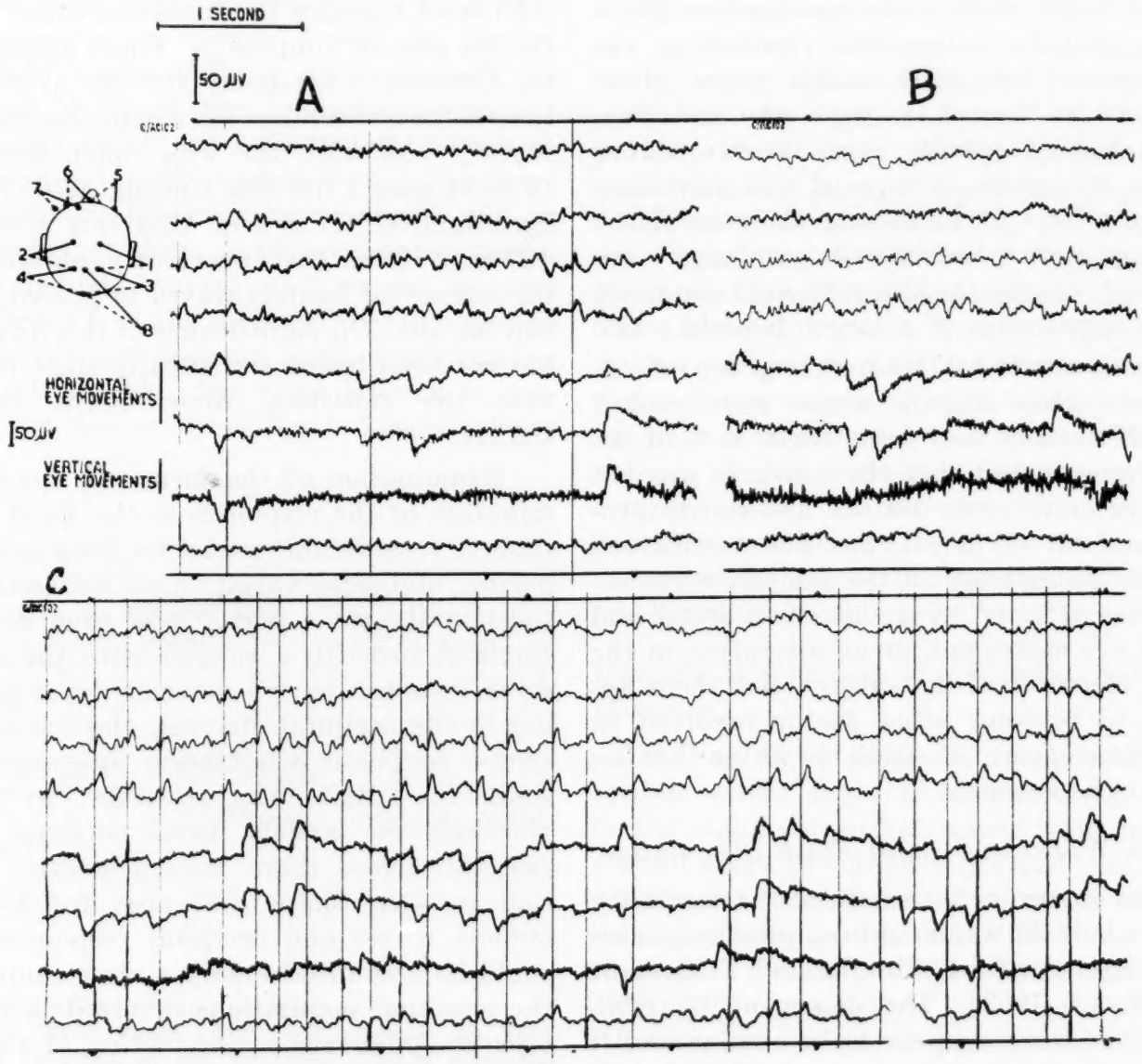

Fig. 5

A. Subject studying small detail of a picture.
B. Subject with the eye movements controlled by following the lines of a pattern. These two examples show few lambda waves.
C. Subject moving his eyes in wide searching movements over the same picture as A, and shows an increase in incidence of lambda waves to eye movement.

There was some variation in the duration of the waves, as there was in shape and amplitude and a more detailed investigation of these changes is in progress. The greatest number of lambda waves seen under test conditions during one second was 5, but usually there were 3 or 4.

In the records of 3 subjects who had very good lambda waves on some occasions, but who at other times showed the waves with much less clear definition, it was found that ordinary lambda waves were seen when for a period of time, the subject studied a picture minutely (fig. 5). When he kept his eyes moving in larger and more searching movements over the whole of the same picture for a further period of time, this resulted in the appearance of very good lambda waves. However, only in these 3 subjects who had fluctuating but potentially good lambda waves, did this alteration in type of eye movement have the effect of increasing their incidence and amplitude: individually a larger eye movement was not itself a sufficient condition for the appearance of a larger lambda wave.

It was concluded from this group of experiments, that lambda waves were evoked only when there had been some sort of an eye movement, but that the converse was not true: eye movements did not necessarily produce lambda waves. It was not ascertained whether the increase in the lambda wave activity was affected by a change in speed and type of eye movement, or an alteration in the mental alertness of the subject, but there appeared to be some other factor involved in the enhancement of lambda waves besides simple eye movement.

Lambda Waves and Light Flash Stimulation.

Some observers have noticed the similarity between lambda waves and occipital responses evoked by light flash stimulation (Y. Gastaut 1951; Evans 1953). The shape and distribution of the waves appear to be similar and it has been noted that lambda waves are often more easily evoked following flicker stimulation. Experiments were performed to compare the latency of these occipital responses to light flashes, with the latency of lambda waves to eye movements; the light stimulus was a single flash from a photic stimulator, usually given infrequently, i.e. with at least 5 sec. between flashes. Some experiments with frequent stimuli at about 3/sec. are also described.

The average latency of the occipital response to a flash, involving 1,104 measurements, was 70 msec. taken over 27 subjects who showed the response clearly, a figure that is within a group of latencies obtained by Cohn (1952) in his work on latency measurements of the cortical response to photic stimulation. The average latencies for each individual subject ranged from 54 to 81 msec. The measurements for eyes open and eyes shut have been calculated together for these and other results for the sake of simplicity. There appeared to be, however, a tendency for the average latencies from these and later experiments, to be slightly less with the eyes open than shut (2 to 14 msec.) but this finding needs further investigation. It is seen that this average is different from that previously obtained for the latency of lambda waves to preceding eye movements. The significance of this difference has not been tested statistically since in addition, the statistical distributions are not similar.

Examination of the form and spatial distribution of the responses in the EEG record showed considerable variation from person to person, and some variation on different occasions in the same person and even during a single record. In a subject with the lambda wave response to eye movement predominating in the occipital channel, the occipital response to photic stimulation appeared to be similarly distributed. However, in a subject with the lambda waves maximal in the parietal areas, there was a greater variation in wave shape and area for both the lambda waves and occipital responses. This could be accounted for by a close coupling of the neuronal populations involved in the two separate phenomena. Activation of the light response group might then excite the neurones of the lambda wave group. If these groups were spatially overlapping (occipital lambda wave) the pattern would be consistent, but if they were spatially separate (parietal lambda wave) the coupling might be less constant and interference could result in a less consistent pattern.

An attempt to investigate further the relation between the lambda wave response to an eye movement and the occipital response to a single flash, is being carried out by the

use of signal superimposition techniques. In this method any consistent response to a stimulus is differentiated from activity randomly related to the stimulus, by superimposing on the same photographic plate successive traces of a C.R.O. display which is recording the required signal, the time base being triggered by the stimulus (Dawson 1947). The resulting superimposed responses obtained with a light flash stimulus are compared with the picture of lambda waves similarly obtained, with the time base of the display triggered by the eye movements which are here thought to act as the stimulus for the lambda wave. This type of experiment has only been carried out on one subject to date (with parietally predominant lambda waves) and as can be seen from figure 6 B the material so far obtained is of interest but does not conclusively answer the question. The dissimilar latency is confirmed. A close study of figure 7 which shows a 4 channel C.R.O. display recording responses to single and repetitive flashes of light, auditory stimulation (q.v.) and also lambda waves to eye movements, suggests that in fact, the lambda wave may be a component of the light flash response. More investigations of this kind are to be carried out.

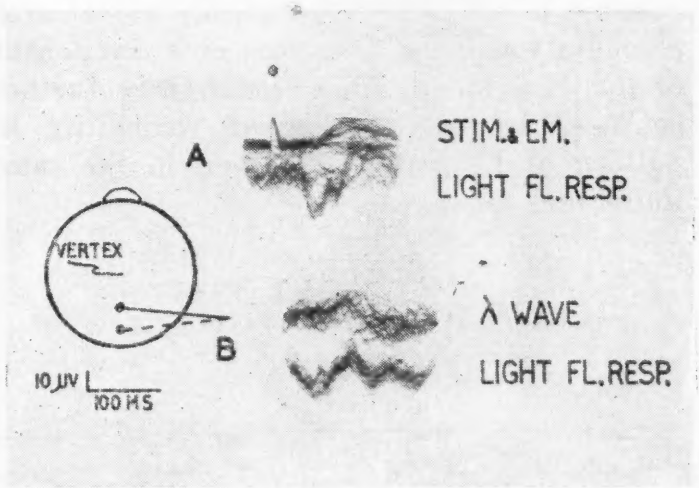

Fig. 6

Trace integration by superimposition.

A. Upper trace shows photo cell response to light flash followed by the electrical change produced by vertical eye movement.

Lower trace shows EEG response from electrodes shown.

B. Upper trace shows lambda wave, the display time-base being triggered by the eye movement preceding it.

The lower trace shows the response to light flashes at about 1.5 /sec. the time-base being triggered by the photo cell response.

These two traces were recorded at different times on the same area of film, but since in each the time base is triggered by the causal event, they are shown in comparable time relationship to this event.

B is displaced with reference to A so that the stimulus mark in the upper trace of A roughly corresponds to the position of the equivalent stimulus in B.

A further consideration is that the flash of light could cause an involuntary blink or eye movement resulting in a lambda wave which might mix with the true occipital response to the light stimulus. The resulting pattern could easily produce confusion. To test this point a superimposition record was taken, one channel recording the EEG, the other recording the photo cell response to the flash together with the eye blink (fig. 6 A). The photograph shows that the eye blink is in fact delayed until after the beginning of the occipital response, by a latency which is constant from stimulus to stimulus. The component of the occipital response which is comparable to a lambda wave (fig. 6 B) could therefore not be produced by the eye blink unless the latency of this mechanism was very much reduced.

Lambda Waves and the Waking K-complex Response.

It has been suggested previously that lambda waves might be in some way related to the similar occipital waves seen during a certain stage of light sleep (Roth and Green 1953), and that these latter waves also had some features in common with those of the K-complex in sleep (Roth, Shaw and Green 1956). The generalized "vertical spike" or "K-complex" response to a peripheral stimulus, besides being evoked in sleep may also be obtained in the waking state, though usually with a smaller amplitude so that it is not easily differentiated from background activity (Gastaut 1953; Bancaud 1953; Roth, Shaw and Green 1956). Although this complex is phase reversed at the vertex it is widely distributed and extends to the occiput where a large though variable component is often seen (fig. 8). The question arose as to whether the occipital response to a single light flash stimulus was a response in this

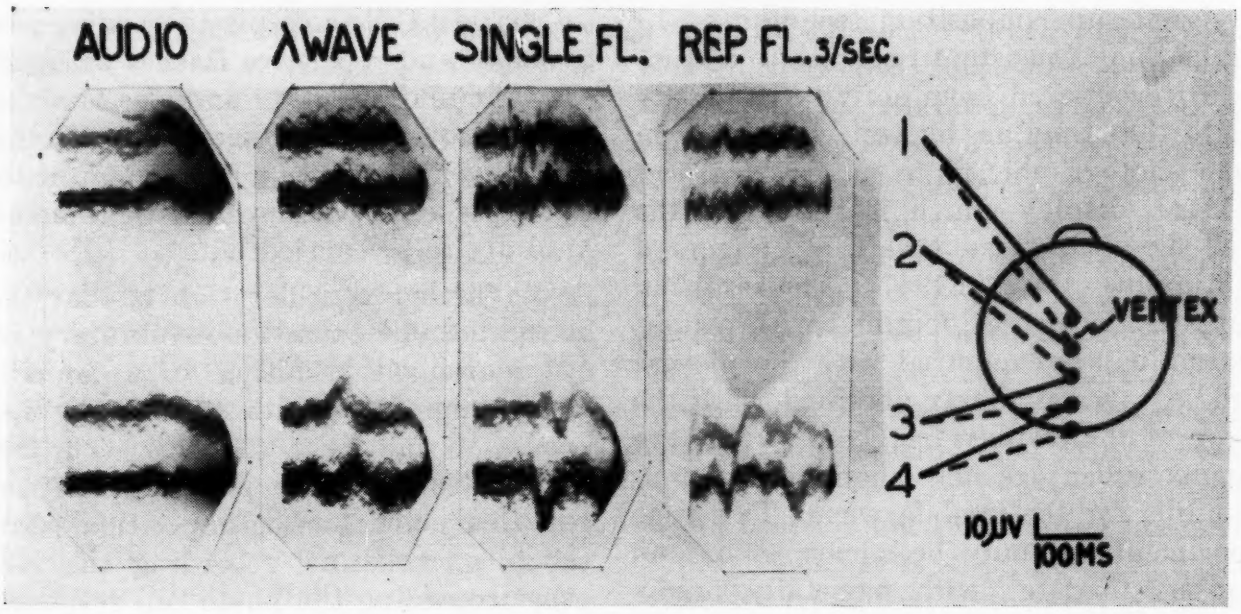

Fig. 7

Trace integration by superimposition using a 4 channel display, of the various phenomena discussed. These are to illustrate wave form only, the time relations to the start of the trace not being comparable.

area mediated solely by visual pathways, or whether it was a component of the K-complex, which may be evoked by spaced single light flashes and also other forms of stimulation.

In fact, in the work described above on the measurement of the latency of the occipital response to a light flash, a K-complex very often occurred. It was therefore not always possible to say whether a purely visual area response was being measured or a component of the K-complex. This situation is further confused by the very great variability in pattern of responses seen even in the same individual.

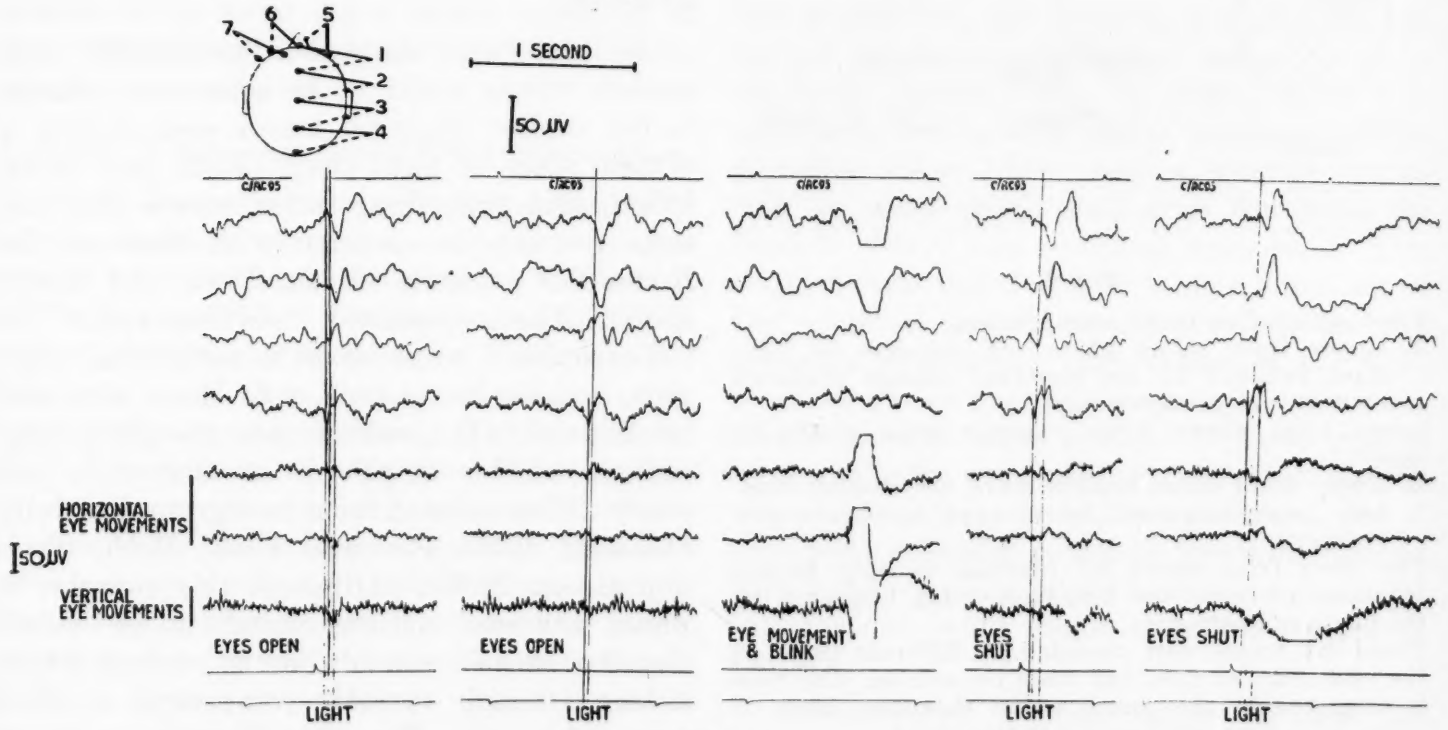

Fig. 8

Responses to single light flash stimulation in one subject, with the eyes open and eyes shut and the appearance of a blink. Note the double occipital component in this subject.

Measurement of the latency of the K-complex induced by a single light flash showed an average latency of 70 msec. involving 472 measurements over 18 subjects. Vertex or prevertex channels only were used for the measurements to avoid interference with occipital patterns or frontal eye movement artifact. Average latencies for each individual subject ranged from 57 to 85 msec. This mean latency is seen to be the same as that obtained for the occipital response to a flash of light.

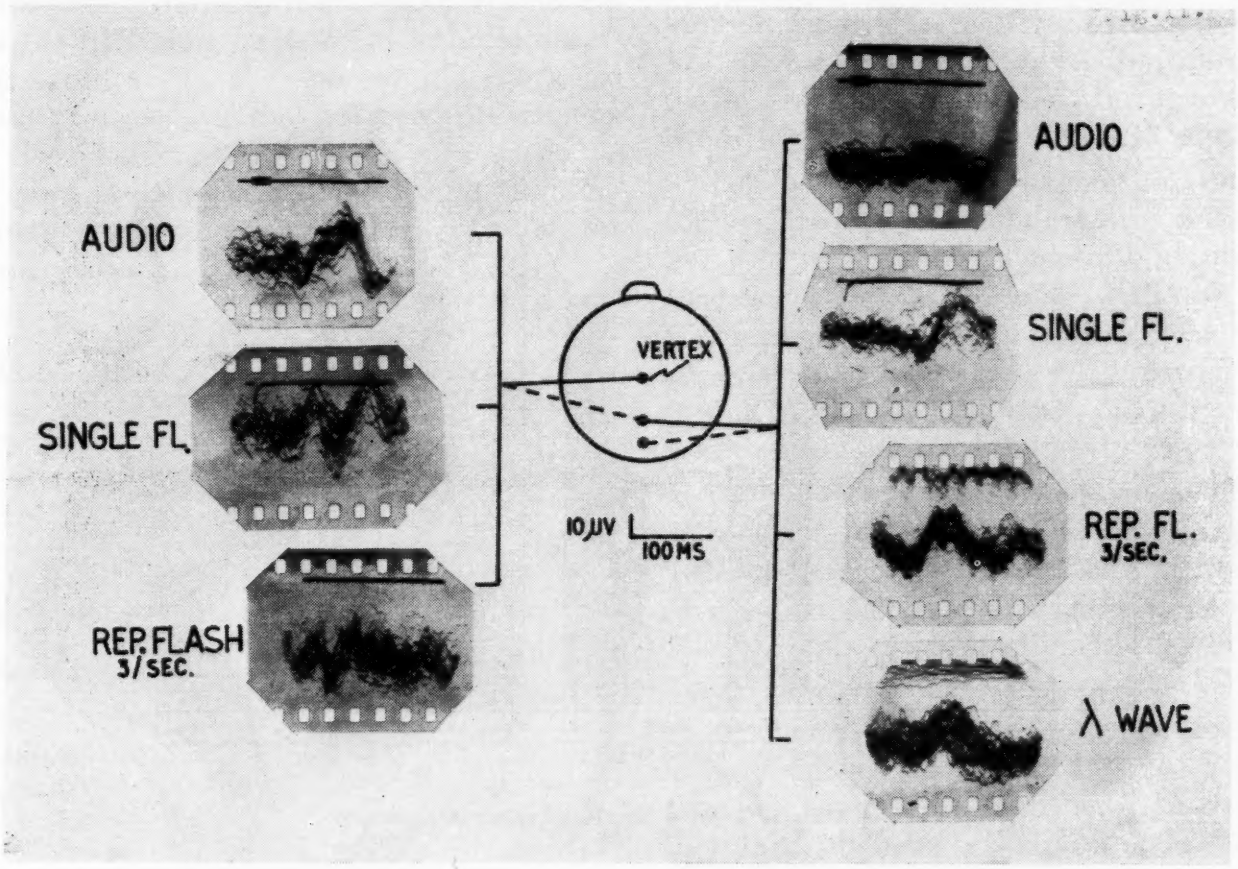

Fig. 9

Trace integration by superimposition showing the various phenomena discussed. Where the stimulus is not shown it triggered the time-base; where it is shown, the time-base commenced a fixed interval before the stimulus. In the former case, the traces are displaced to show roughly the time relationship to the latter.

There was some evidence that the occipital component to light stimulation, might be occurring independently of the K-complex. It showed considerable variation in being present or absent from the K-complex and occasionally it was elicited alone; in some people it showed a tendency to appear as a double wave more often than it appeared as a single wave. Apart from the fact that this occipital wave could occur without any apparent vertex disturbance, it was possible to distinguish the occipital component of the vertex focal K-complex from any other concomitant of the flash stimulus by increasing the flash frequency. Since the K-complex has a refractory period of about 1-3 sec. (Roth, Shaw and Green 1956) light stimulation at more than 1 flash per second eliminates its contribution to the overall pattern. This of course is the familiar situation in routine photic stimulation.

If the occipital response to isolated light flashes is independent of the occipital component of the K-complex, then a different occipital pattern should be observed when the K-complex is evoked by auditory rather than visual stimulation.

Measurement of the vertex response to auditory stimulation with a 20 msec. pulse of 1000 c/sec. gave an average latency of 69 msec. (435 responses over 15 subjects), which is

about the same latency as for the light flash stimulus; averages for each individual subject ranged from 52 to 89 msec. The variability of the responses again made differentiation difficult when the straight EEG was examined. An occipital wave was present in the auditory K-complex, but in most cases was not as clearly defined as when it was evoked by light flash stimulation. However, the integrated response produced by the superimposition technique previously mentioned showed that the post vertex response of the K-complex evoked by light flash and auditory stimulation were complex and did not appear to be identical (fig. 9).

Both the waking K-complex to auditory and that to single flash stimulation were most easily evoked in the younger subjects aged 18 to 25 years. In most people however, at 1 stimulus in about 7 sec., the complex appeared inconsistently, would be evoked for several stimuli and would then spontaneously miss, for no apparent reason. This did not seem to be related to accommodation of the subject. It appeared, however, that a stimulus of sufficient intensity or contrast from the normal conditions was necessary to evoke the complex, the intensity depending upon the subject. This was adjusted to be slightly less than that of a stimulus causing a startle reaction.

The histogram of figure 10 shows how the average latencies of each subject measured, are distributed in each of the 4 stimulus groups.

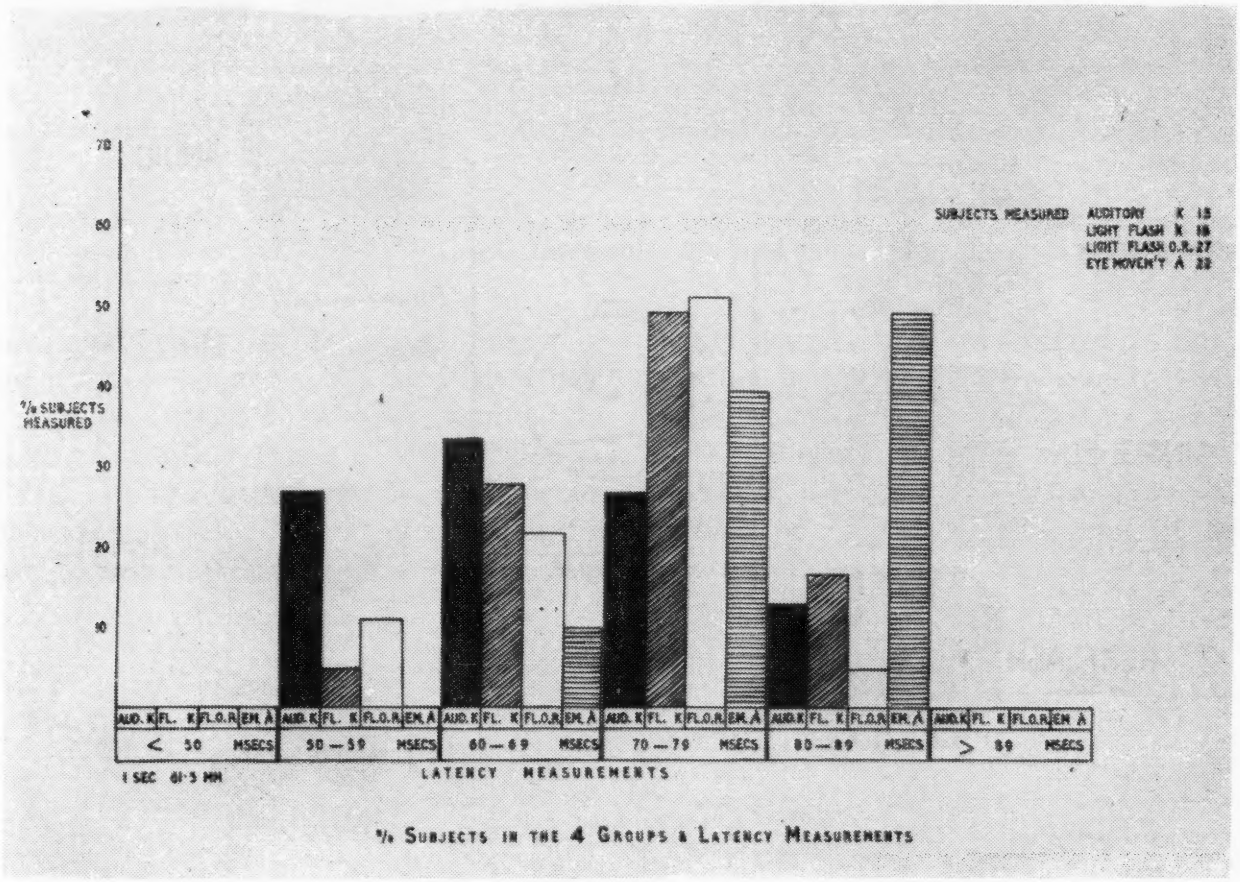

Fig. 10

The distribution of subjects within the range of latencies encountered in each of the 4 stimulus groups. (FL.O.R. signifies flash occipital response to photic stimulation.)

Out of the 23 subjects tested for auditory, flash and eye movement stimulation, 8 people could be classified as showing very good responses; 3 subjects showed very good responses to all stimuli. Another 2 with very good auditory and light flash K-complexes showed poor lambda waves on eye movement. It also appeared that 2 people having very good lambda waves had poor auditory and light flash responses and that one person with fair light

flash responses and very good lambda waves, had very poor auditory K-complexes. It seemed therefore that there was no direct relationship between the phenomena.

It appeared easier to evoke a light flash K-complex than an auditory one, as of the 18 subjects showing a complex clear enough to be measured, 6 had no auditory K-complexes that were measurable, whilst each of the 15 people having an auditory response, also had a light flash K-complex, except for one person who had high background activity. There was a fluctuation in amplitude of each type of response to different methods of stimulation.

In table I the averages of all measured latencies for each of the different phenomena have been compared. These measurements show very small scatter, considering the non-symmetric range of average latencies for lambda waves.

TABLE I

TABLE SHOWING THE MEAN OF ALL MEASUREMENTS

	Waking Auditory K.	Flash K.	Flash Occ. Resp.	E.M. λ
Mean Latency msec.	69	70	70	82
No. Measurements	435	472	1,104	3,971
No. Subjects Measured	15	18	27	22
Total Subjects Tested	29	27	33	29

Although lambda waves were enhanced by certain types of movements of the eyes, especially when the subject was interested in the task, the waves did not appear with all eye movements, and their occurrence depended largely on the state of alertness of the subject combined with the nature of the task. The different phenomena described above appeared at first to have no direct relationship, but on close examination of the waveforms, some overlap of the components could be discerned. This fact, together with the similarity of the latency measurements suggest that lambda waves may have more in common with some part of the arousal mechanism than with eye movements alone. This would be substantiated by the previous observation that some features of lambda waves are similar to the occipital waves that are seen during the stage of sleep when K-complexes can best be evoked.

SUMMARY

1. A series of experiments involving different types of eye movements and visual tasks, using 94 normal subjects showed that lambda waves were best seen when the subject looked at a detailed picture with interest. Eye movements were a necessary but not sufficient condition for the production of lambda waves.

2. Comparisons were made of the latency for eye movement lambda waves with the latency of occipital responses to stimulation by flashes of light, and also with the waking K-complexes to light flash and auditory stimulation. The latency measurements of the different types were similar, but the lambda waves showed a slightly longer latency.

3. There was much variation in the shape, amplitude, and incidence of each response to a stimulus, which occurred with all four types of phenomena. Subjects showing a good response to one type of stimulus did not necessarily have a good response to the other types.

4. The different phenomena appeared to have complex wave forms and no direct relationship could be established. However, the fact that on close examination of the wave forms, some of the components appeared common to each of the phenomena, combined with the closeness of the latency measurements, suggest that lambda waves may have more in common with some part of the arousal mechanism than with simple eye movement.

Thanks are due to Dr. Joshua Carse, Medical Superintendent, for his permission to carry out this work, and also to Mr. John Shaw for his considerable help, and to the subjects who have co-operated so patiently.

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CLINICAL AND LABORATORY NOTES

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ELECTROENCEPHALOGRAPHY IN A CASE OF CEREBRAL VASCULAR MALFORMATION

(Report of a case)

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Clinical manifestations of intracranial arteriovenous malformations are varied, obviously depending upon the size and location of the anomaly as well as the amount of bleeding. The diagnosis of this condition is usually made on the basis of the clinical course and arteriography. The following is a report of a case with provocative electroencephalographic findings.

METHODS

Electroencephalograms were recorded with a type D Offner machine using 18 electrodes with 10 different montages, 3 of which were common reference and 7 series bipolar.

CASE HISTORY

E. M. is an 11½ year old Puerto Rican white male who was perfectly well until March 8, 1956 when he suddenly complained of a frontal headache, malaise, anorexia and a sensation of ''warmth'' with vomiting after eating. These symptoms became more severe and a local physician advised hospitalization because of ''anemia''. However, the boy was kept at home and the symptoms progressed. On March 10, 1956 another physician diagnosed ''meningitis''. On March 10, 1956, the patient was first seen at Bellevue Hospital where he was noted to be afebrile, very lethargic, with positive Kernig and Brudzinski signs, a rigid neck and a mildly inflammed throat. Lumbar puncture revealed an initial pressure of 230 mm H_2O, with normal C. S. F. findings. In view of these findings, it was felt that the patient had a mild viral upper respiratory infection with secondary meningismus.

The signs and symptoms became more severe and he was admitted to Bellevue Hospital on March 11, 1956 with a temperature of 100°F., pulse 64/min., respiratory rate 20/min., and blood pressure 96/60 mm. Hg. He was markedly lethargic and responded sluggishly to questioning and painful stimuli easily lapsing into light sleep. His speech was slurred and nasal in quality. Positive findings on physical examination were a rigid neck, minimal ptosis of the right eyelid, dilatation of the right pupil, bilateral ankle clonus and positive Babinski's, Kernig's and Brudzinski's signs with slight weakness of the left arm and facial muscles.

White blood cells numbered 10,000 with normal differential. C. S. F. was clear, with an initial pressure of 250 mm. H_2O which rose to 300 mm. H_2O on jugular compression. It contained 1 mononuclear cell per mm^2, 28 mg. per cent of protein, 80 mg. per cent of sugar and no bacteria on culture. On March 12, 1956 a. m. the patient was much more alert and responded readily to questioning and examination. The clinical picture was changed. Minimal athetoid movements of the left hand were now present. There was no weakness and no ankle clonus, and Babinski's sign present only on the left. Corneal reflexes were also present. In the afternoon of the same day the right ptosis was absent, pupils equal, muscle power equal with persistent left hand athetosis and questionable left Babinski and moderately positive Kernig and Brudzinski signs.

The impression at this time was that the patient had either meningitis of unknown origin, intracranial neoplasm or vascular anomaly.

On March 13, 1956 there was no change except for the disappearance of the Babinski sign. White blood count was 6,950 with a normal differential.

On March 15, 1956 the C. S. F. was clear with initial pressure of 180 mm. H_2O. It contained no cells, protein 40 mg. per cent, sugar 72 mg. per cent and no bacteria on culture. By March 19, 1956 the physical examination was entirely normal and the patient showed an almost complete recovery. Two days later, however, he experienced a sudden onset of vomiting, frontal headache, extreme lethargy with

1 This laboratory is supported by the Sister Elizabeth Kenny Foundation.

sluggish responses and clouding of the sensorium. Physical examination revealed ptosis of the right eye, mild weakness of the muscles of the left arm and face, right Babinski's sign, no bruits audible, vital signs normal, optic discs normal on fundoscopic examination. C. S. F. pressure was 280 mm. H_2O; the fluid was markedly xanthochronic but sterile with a protein of 325 mg. per cent and sugar 69 mg. per cent as well as 4 crenated red cells, 21 mononuclear blood cells, 30 mononuclear cells, 185 ghost cells and 380 mg. per cent of protein.

Consultation with a pediatric neurologist on April 9, 1956 revealed that the child had a left motor weakness and a left homonymous hemianopsia. His impression was that the patient had a right hemisphere lesion, neoplasm or arteriovenous anomaly probably involving the anterior part of the optic radiation in the temporal lobe.

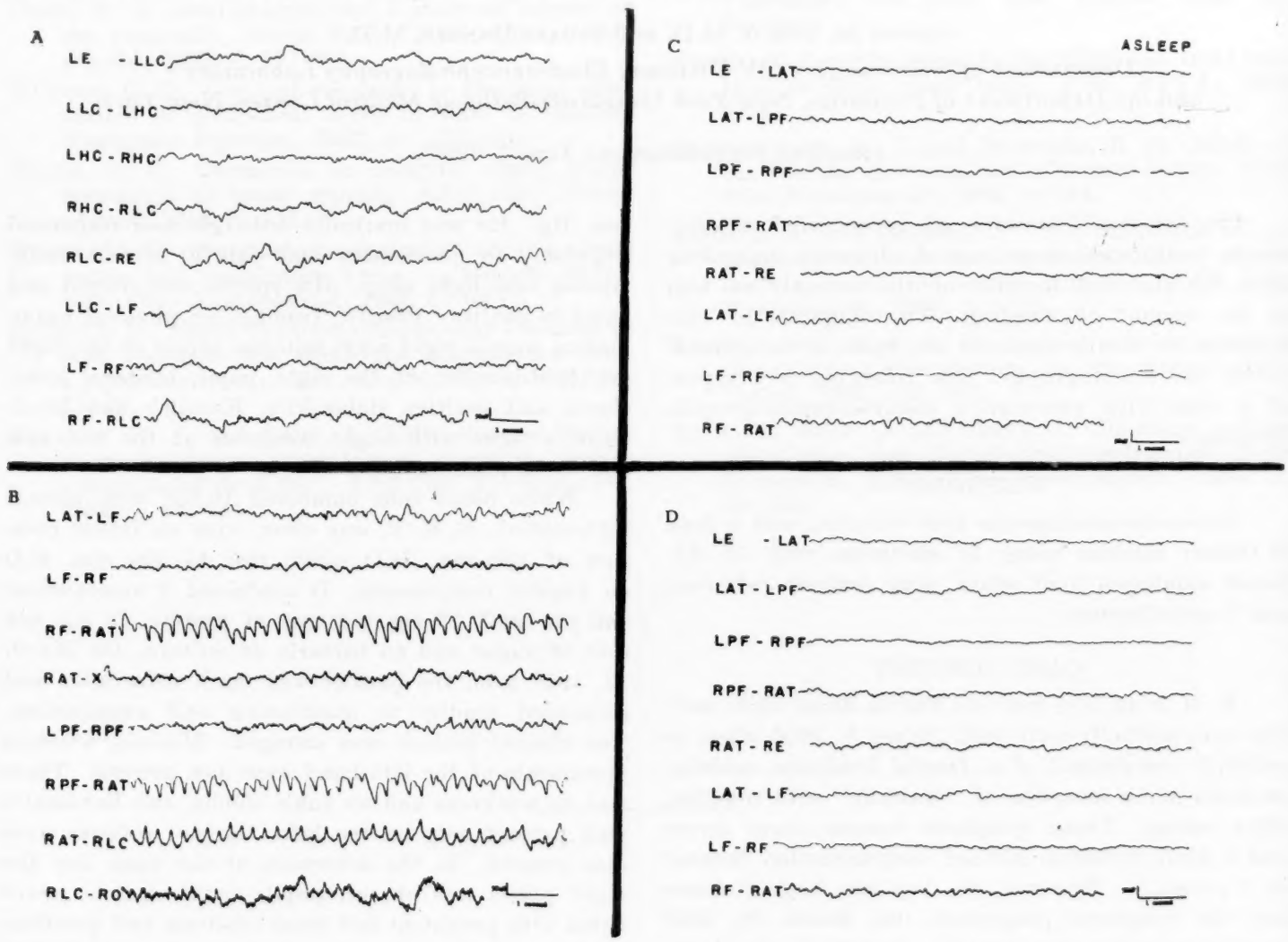

Fig. 1

A. 1st record. Normal sleep. The minimal asymmetry could be granted no significance. LE, left ear, LLC, left low central, LHC, left high central, RHC, right high central, RLC, right low central, RE, right ear, LF, left frontal, RF, right frontal.
B. 2nd record. Grossly abnormal, showing a slow wave focus in the right anterior temporal area. X is 5 cm. inferior to the right anterior temporal lead.
C. 3rd record. Normal sleep record. D. 4th record. Normal sleep record.
Calibration: 50 μV.
Time-scale: 1 sec.

cells. By the next day there was a remarkable improvement and the patient was alert and active with clear sensorium. Neurological examination was entirely normal except for minimal athetoid movements of the left hand. White blood count was 7,100 with normal differential. The first electroencephalogram on March 22, 1956 was normal (fig. 1 A).

On March 24, 1956 the C. S. F. pressure was 250 mm. H_2O. The fluid xanthochromic with crenated red

As there had been a clinical change since the first normal EEG, a repeat was obtained on April 13, 1956 (fig. 1 B).

The report stated: ''This is a grossly abnormal record for the age showing a delta slowing focus on the right anterior temporal area. This is probably due to some organic condition in the right hemisphere most likely the posterior frontal area or the part of the temporal lobe lying just beneath that.''

The same day the C. S. F. pressure was 130 mm. H_2O. The clear sterile fluid contained 4 mononuclear cells/mm.2 protein 61 mg. per cent, and sugar 72 mg. per cent. Left homonymous hemianopsia persisted during hospitalization. A pneumoencephalogram performed on April 19, 1956 was normal. EEG's on May 1, 1956 (fig. 1 C) and on May 17, 1956 (fig. 1 D) were normal. It was specially noted that the slow wave focus was not seen in these tracings. An arteriogram on June 6, 1956 revealed an arteriovenous anomaly in the right temporal region (fig. 2) but because of its inaccessible location surgery was not advisable.

Fig. 2
Angiogram showing a vascular malformation on the right middle cerebral artery.

DISCUSSION

This case emphasizes the importance of serial electroencephalography. It was only on the second tracing of the series that noteworthy findings were electrical and clinical changes. Once this accident malformation was responsible for the concomittant electrical and clinical changes. Once this accident resolved, the patient improved both clinically and electrically.

SUMMARY

1. A case is reported of an 11½ year old boy with an intracerebral vascular malformation on whom 4 serial electroencephalograms were recorded.

2. One of these recordings, obtained at the height of an exacerbation of symptoms helped to localize the lesion; the changes in the electroencephalograms paralleled the clinical course and yielded useful information.

3. The advantage of serial EEG's is emphasized.

Reference: BURLO, G. M. and DANOFF, S. Electroencephalography in a case of cerebral vascular malformation. *EEG Clin. Neurophysiol.*, **1957**, *9*: 705-707.

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A CASE OF PYKNO-EPILEPSY ASSOCIATED WITH UNUSUAL ICTAL EEG RECORD

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(Received for publication: April 18, 1957)

There is an almost complete unanimity of opinion among epileptologists that the typical EEG record which is associated ictally with petit mal epilepsy is a 3 per sec. spike and wave pattern which involves both cerebral hemispheres suddenly, synchronously and symmetrically. The special distribution of this discharge is usually generalized, but tends to be most marked fronto-centrally and may even be localized to this region. Deviation from this typical EEG record has, however, been described consisting merely of minor variations in the topographical localization of the discharge as well as in its rhythm and spike formation. The ictal discharge may have a different topography appearing more in the parieto-occipital region than in the fronto-central one. The spike and wave forms may appear at frequencies slower or slightly greater than 3 per sec. The term petit mal variant was first coined by Gibbs, Gibbs and Lennox (1939) to designate those spike and wave forms which occur at frequencies slower than 3/sec. According to Jasper (Penfield and Jasper 1953, p. 590) the spike formation is the least constant component of the seizure. It may be present in some areas and absent in others. Similarly its relationship to the slow component may be also variable. To our knowledge no other type of EEG record has been described in association with this unique type of centrencephalic seizure. The mere fact that in our case of petit mal epilepsy a totally different pattern of ictal EEG record was encountered seems to us to be sufficient justification for the publication and discussion of this case. The bearing that such a finding may have on the physio-pathogenesis of epilepsy and especially on its clinico-electroencephalographic correlations constitutes another reason for the reporting of this single case.

CASE HISTORY

The patient was a boy, 7½ years old, the youngest of three siblings, born at full term with forceps delivery. The developmental history was normal and the past history was non contributory. The parents are non-consanguinous and the family history is negative for epilepsy or any other nervous or mental disease.

The present illness started at the age of six when he began to experience sudden and temporary lapses of consciousness lasting for a few seconds. During these seizures the patient lost contact with his surroundings and stared vacantly. There was no aura of any type and the fit was not associated with any motor or sensory phenomena or loss of postural tone. The disturbance of consciousness was apparently complete, as could be judged from the fact that during this time the patient did not respond to questions and there was complete cessation of all voluntary as well as semiautomatic or even automatic movements. These fits recurred daily with a frequency varying from 3 up to 50 per day. It was noticed that when the fit persisted more than about 15 sec. the patient displayed certain automatic movements consisting of tapping first with the hands and a few seconds later with the feet. These automatic movements were short-lived and stereotyped throughout the whole seizures. The recovery of consciousness was abrupt and was not associated with any of the well known post-ictal sequelae. Nocturnal enuresis occurred most of the nights, but there is no history of either sleep talking or walking. In between the attacks the patient was perfectly normal in every respect and was described by his parents as quiet, emotionally stable and intelligent. His school record was satisfactory.

The general physical and neurological examination of this patient did not reveal the presence of any abnormality. On hyperventilation it was noticed that the fits could be easily and regularly precipitated and were found to be identical with those described by the parents. The child has complete amnesia for the entire period of the attack including the automatisms.

Routine laboratory investigations were essentially negative and plain X-ray of the skull did not reveal the presence of old injury or other pathological abnormalities.

Electroencephalography. Records were obtained with a Grass (model 111) six channel apparatus and the bipolar method was used. They revealed the presence of an alpha rhythm of 9 c/sec. which blocked normally to eyes opening. The alpha rhythm was mixed with occasional slow theta waves which are known to be normally present at this age. There was no evidence of focal abnormality or of any spontaneous subclinical or EEG seizures.

On hyperventilation a clinical fit was precipitated, which was noticed a few seconds after the appearance of a gradually building up generalized discharge of bilaterally synchronous and symmetrical slow waves of high amplitude and irregular form and rhythm. The discharge consisted of a mixture of slow alpha, theta and delta waves, i.e., frequencies ranging from 3 to 7 per sec. The staring lasted for a period of 10 to 15 sec., followed by the automatic movements. It is noteworthy that the automatic movements of the hands and feet appeared at the end of the EEG discharge and continued for many seconds (12 to 20) after the EEG had returned to absolute normality. The same findings were obtained several times on repetition of the test. When the fit was short-lived (less than 10 sec.), it was not followed by automatic movements. It is important to mention that following some of these hyperventilation tests the same typical EEG seizures appeared without any associated objective or even subjective manifestations of clinical epilepsy. This last finding substantiates the view that epilepsy may appear in an abortive, subclinical or purely electrical form.

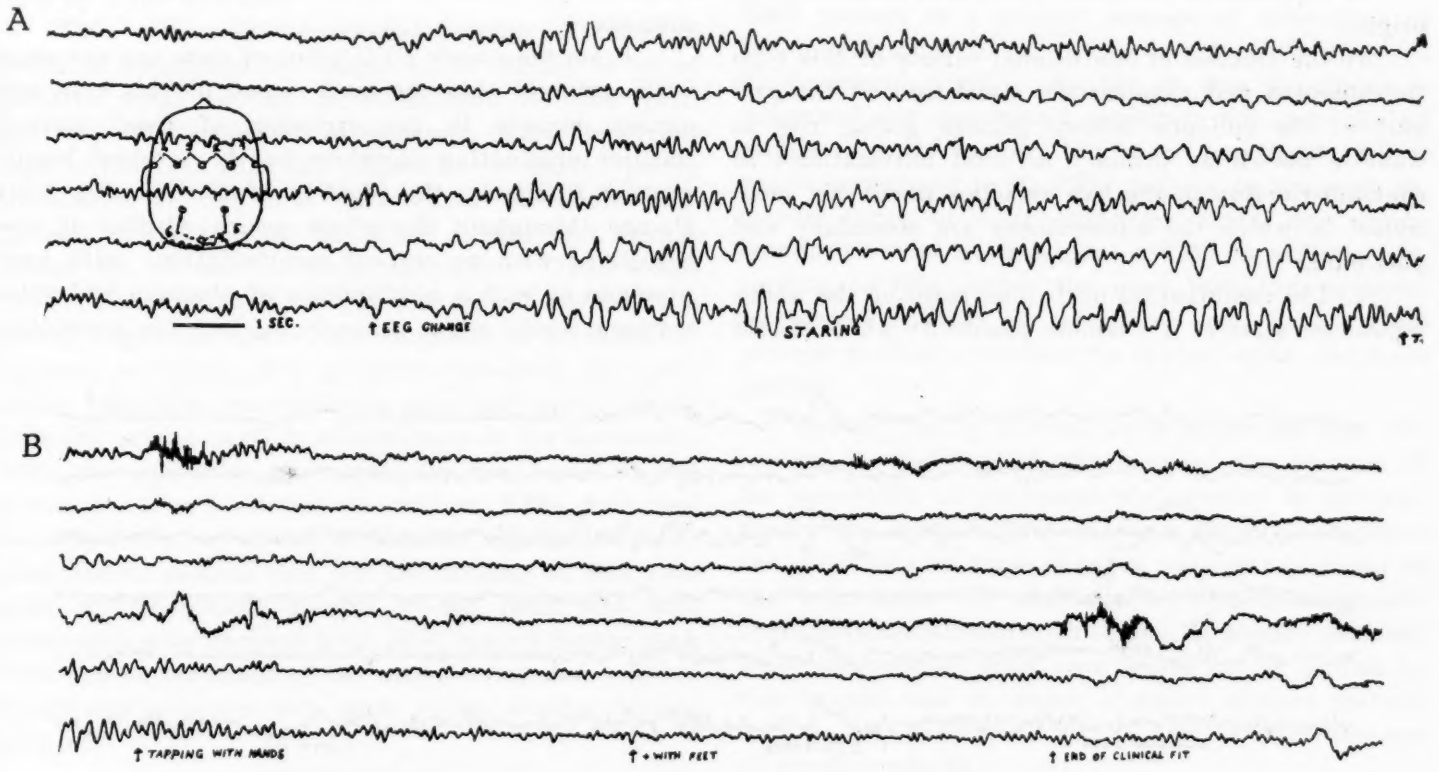

Fig. 1

Ictal record after hyperventilation showing the irregular slow waves together with the time relationship between the onset of the EEG changes, the absences and the automatic movements. (B continuation of A.)

Treatment. On the assumption that this was a case of petit mal epilepsy, the patient was given Paradione (oxyzolidene-dione). Following the administration of 3 capsules of Paradione per day, we noticed gradual and marked improvement, as judged from the diminishing frequency and severity of the seizures. This effect appeared after five days and was maintained throughout the whole period of treatment. To exclude the question of coincidental and spontaneous improvement, the drug was intentionally stopped for a few days during which the seizures recurred with increasing frequency and severity and were again controlled with resumption of drug therapy. It is worthy of note in this connection that other antiepileptic drugs including barbiturates, hydantions and mysoline were tried without avail.

COMMENT

The clinical analysis of this case revealed clearly the presence of epileptic seizures of the minor or rather minimal type which were characterized by two main groups of symptoms: first, disturbance of consciousness of sudden onset, brief duration and mild degree constituting what is known in epileptic terminology as "absences" and secondly, involuntary semipurposive movements which were simple in their character and stereotyped in their pattern, constituting what is known as automatism.

Confronted with this clinical picture and without the aid of EEG we were forced to think of four diagnostic possibilities which in order of their probabilities were as follows:

1. Petit mal seizures of the classical subcortical centrencephalic type which as is well known may be manifested primarily in their ictal phase by pure

absences and secondarily and post-ictally by automatisms.

2. Focal cortical seizures originating in silent areas of the brain and with secondary activation or firing of the centrencephalic system (secondary bilateral synchrony of Jasper (Penfield and Jasper, 1953, p. 612). Like the former seizure, this type of cortical seizure may also be manifested primarily and ictally by absences and secondarily and post-ictally by automatisms.

3. Psychomotor seizures, of cortical or subcortical origin.

In the amnesic or confusional variety of this type the absences and automatisms constitute an integral part of the epileptic seizure pattern giving rise to what is known as primary or ictal automatisms in contradistinction to the two varieties previously mentioned in which the automatisms are secondary and post-ictal.

4. The combination of two or more of the above mentioned seizures is a remote possibility which should be considered in the differential diagnosis of such a case.

Our preference for the pre-electroencephalographic diagnosis of centrencephalic seizure of the petit mal type in this case was based on the following criteria:

(*a*) The young age of the patient.

(*b*) The daily occurrence of the seizures and especially their marked frequency which amounted in many occasions to fifty or more per day.

(*c*) The extreme brevity of the fits which never exceeded 30 sec.

(*d*) The complete absence of auras of any type.

(*e*) The typical clinical picture, consisting of the classical absences.

(*f*) The sudden return of consciousness without any confusion, sleepiness or any of the other common post-epileptic symptoms.

(*g*) The absence of any associated personality or behavior disorders which are generally accepted to be as rare in petit mal seizures as they are common in psychomotor seizures.

The fact that the seizures were markedly controled by Paradione as well as readily and regularly precipitated by hyperventilation constituted additional corroborative evidence in favour of petit mal epilepsy. It should be stressed in this respect that although we favoured the diagnosis of petit mal epilepsy, we were not able to exclude on clinical grounds and with certainty other possibilities of either focal cortical seizures, psychomotor seizures or a mixed type of seizures.

From the purely EEG point of view one can state with certainty that the ictal record of this case was almost decisive in the exclusion of focal cortical seizures originating anywhere in the cerebral hemispheres. Similarly, the identity of the episodic EEG change throughout the whole record whether it was associated with no clinical manifestations, with pure absences or with a combination of absences and automatisms would argue strongly against the possibility

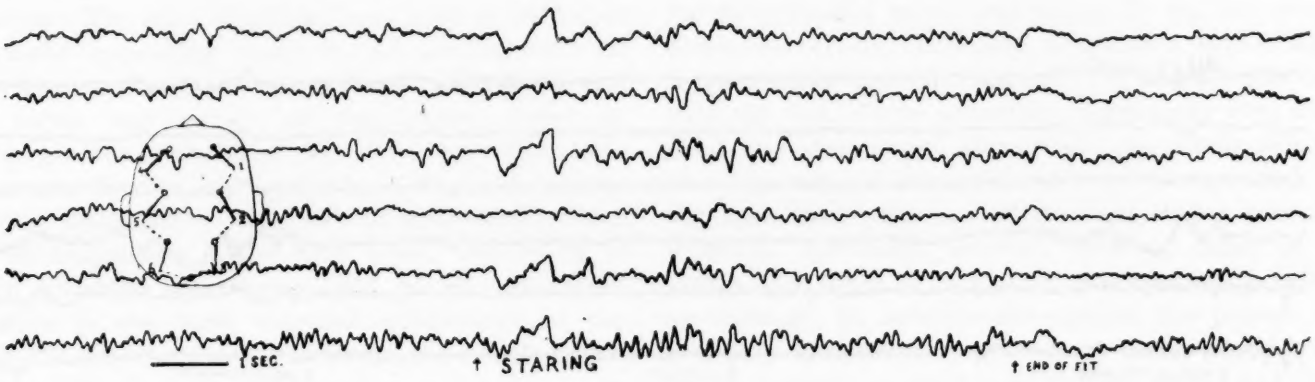

Fig. 2
Ictal record after hyperventilation showing the same irregular slow waves in association with absences without automatism.
N.B.: The same EEG record was obtained without either absences or automatisms.

of a mixed type of seizures in this case. Notwithstanding its value in these respects the ictal changes *per se* were of no help in the differentiation between petit mal seizures and psychomotor seizures of the subcortical type and this for the simple reason that these ictal changes did not conform in their pattern to the classical changes associated with either. It is needless to say that the ictal record of this case differed from the classical pattern of petit mal epilepsy. It similarly differed from that of psychomotor epilepsy by the absence of the pre-ictal isoelectric changes as well as post-ictal exhaustion phenomena which are known to characterize EEG changes of psychomotor epilepsy.

Although neither clinical nor EEG changes *per se* were decisive in the differentiation between these two types of seizures, namely petit mal seizures followed by post-ictal automatism and psychomotor seizures associated with disturbance of consciousness, it will

be noticed that a correlative study of the clinical and EEG changes of this case was of great help in this respect. Such a study has revealed the presence of certain differential points which if considered collectively would undoubtedly favour the diagnosis of centrencephalic seizures of the petit mal type as against psychomotor seizures of primary subcortical origin. The first and most important of these is the fact that the abnormal EEG changes in this case have preceded the appearance of disturbance of consciousness by a few seconds.

This clinico-electroencephalographic differential point is considered by Jasper *et al* (1951) to be of decisive value in the differentiation between petit mal type and psychomotor epilepsy. More important still is the fact that the automatic or semipurposive movements in our case have almost invariably appeared at the end of the EEG seizure and always lasted for 15 sec. or more thereafter. This would favour their post-ictal origin and would constitute a strong argument against the diagnosis of psychomotor epilepsy in which, as is generally accepted, the automatic behaviour constitutes a part and parcel of the epileptic seizure and is synchronous in its occurrence with the epileptic discharge. On the basis of the above mentioned clinical as well as EEG data and especially the correlation of the two together, we felt justified to assume that we are dealing in this case with centrencephalic seizure of the petit mal type associated with unusual ictal EEG record rather than with one or the other of the above mentioned seizures which may give rise to a more or less similar clinical picture.

DISCUSSION

Enough has been said to prove beyond any reasonable shadow of doubt that the clinical features of this case conform in every respect to the clinical variety of petit mal epilepsy known by the name of pykno-epilepsy or petit mal seizures of the minimal type. The only peculiarity which we feel is in need of elaboration and speculation is the unusual ictal EEG record which, to our minds, has not been recorded before and which we feel may prove of value in the elucidation of the exact physiopathogenesis and especially the clinico-electroencephalographic correlation of this type of seizures.

As far as our knowledge of epilepsy goes, these unusual ictal EEG changes can be explained on the basis of one or the other of the following three theories:

A. An anatomical hypothesis implying a variation in the topographical localization of the centrencephalic epileptogenic focus and/or in the direction of propagation of its discharge.

According to this hypothesis, our case would constitute a hitherto undescribed clinico-anatomical variety of centrencephalic epilepsy of the petit mal type.

B. A physiological one assuming a diminution in the intensity of the epileptic discharge. On the basis of this hypothesis this case would represent the mildest form of petit mal epilepsy in which the clinical picture is identical with that of pykno-epilepsy whereas the EEG record is similar to the interseizure pattern encountered in some cases of petit mal epilepsy.

C. A pathological one attributing the unusual EEG pattern to a greater damage or dissolution of the epileptogenic focus, as has been recently proposed by Grossman (1955). As far as this hypothesis is concerned our case would constitute not only clinical evidence in its favour, but more important still it would correspond in its EEG pattern to the most immature forms of EEG discharges which were experimentally found by Grossman (1955) in animals. According to this author the most immature epileptic discharges consist of irregular slow waves which precede in their evolution the typical spike and wave pattern.

Before closing, a final word should be said concerning the bearing of this case on the question of the specificity of electroencephalography in epilepsy. So far the evidence that has been forwarded against the specificity of these changes was entirely based on the association of similar electroencephalographic changes in association with dissimilar seizure patterns. That the reverse holds true seems to be proved by this unique case in which identical clinical pictures may be also associated with dissimilar electroencephalographic records.

The discussion of this problem should be left at this stage until more cases are collected and completely investigated and until more is known of the physiopathogenesis of the epileptic seizures as well as its clinico-electroencephalographic correlation.

SUMMARY

1. A case of centrencephalic seizures of the petit mal type associated with unusual ictal EEG record is reported.

2. The diagnosis of this case is discussed and its differentiation from the other types of seizures especially psychomotor seizures is detailed.

3. The physio-pathogenesis of this peculiar clinico-electroencephalographic variety of petit mal epilepsy is discussed.

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ANNOUNCEMENT

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THE USE OF NOLUDAR IN PEDIATRIC ELECTROENCEPHALOGRAPHY

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(Received for publication: February 10, 1957)

Various drugs and hypnotics have been used to induce sleep. This report is concerned with the use of Noludar.[1] It is a newly developed hypnotic, distinguished by high therapeutic activity and low toxicity. Noludar is a central nervous system depressant which is non-alkaloidal. It is a piperidine derivative and does not belong either to the barbituric acid or the ureide groups. Chemically, Noludar is 3,3-diethyl-5-methyl-2,4-piperidinedione. Experimental studies with animals and clinical studies with humans reveal that Noludar is distinctly less toxic than phenobarbital. In adults, Noludar is well tolerated and effective with a fairly rapid onset and a short duration of effect. In view of the reportedly quick action of Noludar, it was decided to see how effective this would be as an agent to induce sleep in children referred for electroencephalographic study. It was also investigated from the point of view as to the amount of fast activity produced in the record and as to its quieting influence on those children who are often stimulated by the barbiturates.

METHOD

The Noludar in the elixir form was used. The taste is pleasant to children and not as objectionable as the taste of some sedatives. Furthermore, children are more prone to accept a sedative in the elixir form rather than as a tablet. Preferably, a short period of waking activity was obtained, then the Noludar was administered, followed by a 3 min. period of hyperventilation by those patients who would cooperate. Those patients who appeared to be difficult to handle and the very young infants were given the Noludar prior to the application of the electrodes.

Early in the study an attempt was made to administer a dosage of Noludar which was believed to approximate the equivalent amount of Nembutal which Kellaway and Fox (1952) found effective in their sleep study of children. As more experience with Noludar was gained, the dosage given according to the child's age was as follows:

2	Mo. - 1 yr.	50 mg.
13	Mo. - 29 mo.	75 mg.
2½	Yr. - 3 yr.	100 mg.
4	Yr. - 9 yr.	150 mg.
10	Yr. - 15 yr.	200 mg.

Usually, if sleep had not ensued within 30 min. from the time of the original dosage, half of this dose was again given the patient.

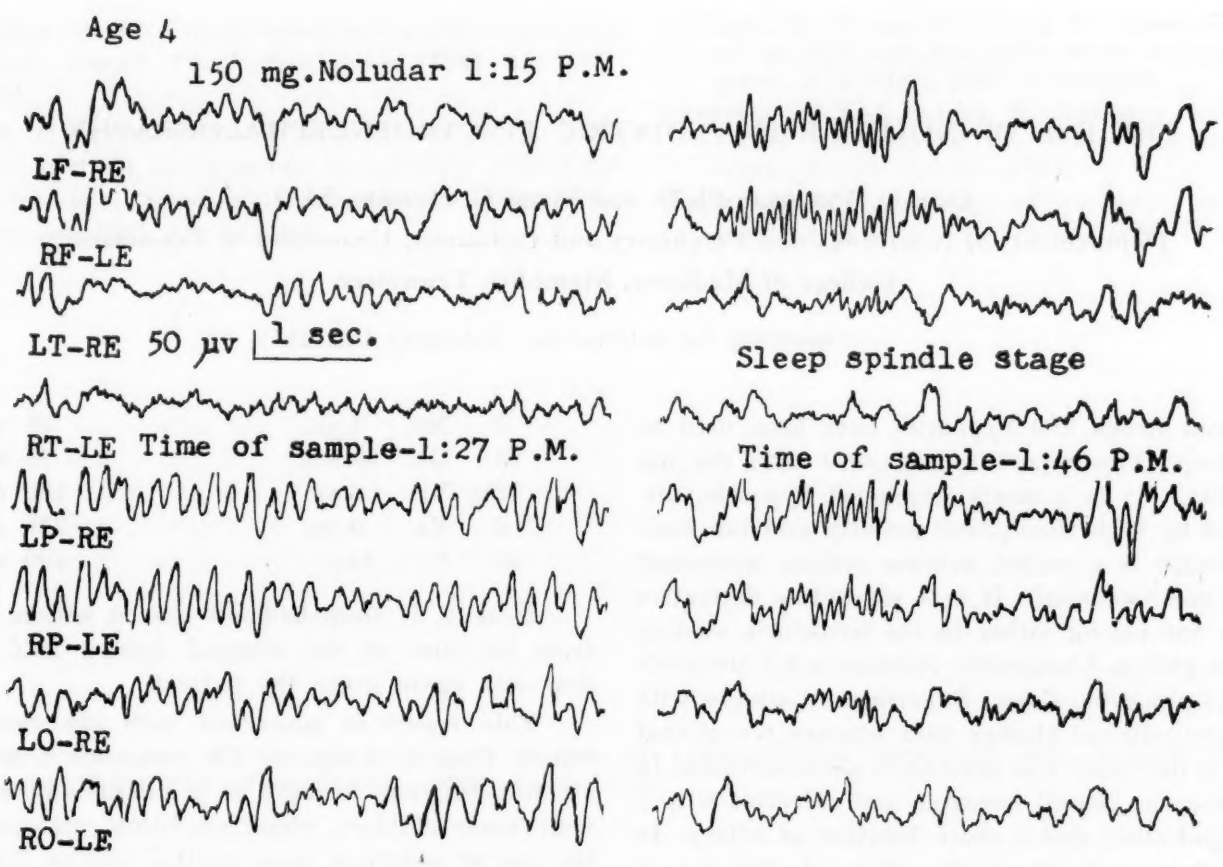
This report is concerned with the results obtained from a study of 278 consecutive EEGs on children between the ages of 2 months and 15 years. Only those children whose condition contraindicated the use of sedatives were omitted during the course of the investigation. No attempt was made to select the patients, although the age, weight, and provisional diagnosis were recorded. One purpose of the study was to evaluate the effectiveness of Noludar on all types of pediatric referrals.

RESULTS

Two hundred and twenty-three of the 278 patients had sleep spindles in their records. The average length of time to obtain spindles in their records was 26.41 min. with an average dosage of 150.90 mg. of Noludar. The average length of time before the termination of the record of the non-sleepers was 51.16 min. with an average dosage of 211.36 mg. of Noludar. Fifty-three of the patients with sleep spindles had repeated doses of Noludar. The second dose generally was about ½ of the initial dose. Forty-three of the non-sleeping patients had repeated doses of Noludar. The average age of the sleeping and non-sleeping groups was approximately six years and weight differences were small but not significantly so.

Thirty-four (71 per cent) of 48 behavior problem referrals slept, 132 (83 per cent) of 160 convulsive disorder referrals slept and 53 (76 per cent) of 70 patients with other CNS disorders slept. Eighty per cent of the total group slept and 81 per cent had abnormal EEGs. This is interpreted as a favorable response to the medication as compared with the results reported in other studies using other sedatives

[1] Noludar used in the study was supplied through the courtesy of Dr. Thomas C. Fleming, Department of Clinical Research, Hoffman-La Roche Inc., Nutley, N. J.



(Gibbs and Gibbs 1946; Kellaway 1950; Kellaway and Fox 1952; Levin 1952; Winfield 1955). This is particularly true since no special preparations were taken with the patients prior to the examination. Since the purpose of this study was not to investigate the clinical side effects of Noludar (that having been done extensively by previous investigators — Loughlin *et al.* 1955), no systematic attempt was

made to collect such data. In a few instances it was noted that a non-sleeping child who was administered rather large doses of Noludar appeared to be a little unstable and dizzy. Very rarely did a child appear to be stimulated by the Noludar, per se. On the contrary, in many instances, those children who in our experience would probably have been stimulated by the barbiturates were quieted by Noludar.

The EEGs in this study were examined with reference to the amount of fast activity present. Of the 278 patients in this study, 186 patients had no fast activity or negligible amounts in their EEGs (fig. 1). Forty-one patients had some fast activity which appeared to be accentuated by the Noludar. There were 38 other patients known to be on anticonvulsant medication (barbiturates alone or in combination with other medication) at the time of their brain wave tracing. In this group, the fast activity present was believed to be either barbiturate induced or else activity characteristic of these children. In most instances the fast activity appeared to be potentiated by the Noludar. Thirteen other patients were believed to have abnormally fast EEGs. As with barbiturates, the fast activity is generally potentiated in drowsiness and light sleep. An analysis of the data would indicate that by giving 200 mg. of Noludar beginning at the age of 8 years instead of 10, as done in this study, would probably increase the percentage of sleep records.

CONCLUSIONS

In general it would appear that Noludar is a good hypnotic for the induction of sleep in pediatric electroencephalography. In the recommended doses, it produces sleep in a reasonable length of time in most patients. Furthermore, it does not generally induce fast activity in the record, although it appears to enhance fast waves already present whether they be barbiturate induced or characteristic of a given patient. Since 81 per cent of the patients had abnormal EEGs, it would appear unlikely that Noludar would be considered a depressant of abnormal brain wave activity. Noludar appears to be particularly effective with behavior problem referrals and with those children who are generally excited by the barbiturates. No significant undesirable side effects were noted during the study, although no systematic attempt was made to investigate them.

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SCALP EEG'S OF PATIENTS RECEIVING ORAL BENACTYZINE [1]

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INTRODUCTION

In recent years there has been increasing interest in a new class of drugs, ataraxics or tranquillizing preparations. It has been postulated that these chemicals have a selective action on the nervous system in that they are believed to act chiefly, or possibly entirely, on basal brain structures — the diencephalon and brain stem.

It has been theorized that the alpha rhythms may be regulated from the brain stem, and that decreased alpha rhythm in the cerebral cortex is associated with the state of being alerted to external stimulation, while an increase in alpha rhythms is related to an absence of alertness. It has been postulated further that some drugs activate this system while others depress it.

Studies and reports on patients who have received some of the better known tranquillizing drugs as oral medication have been few and have been contradictory as to the specific effect, if any, of the drugs on the cerebral rhythms. Several workers have stated that scalp EEG's have shown but few significant changes that could be related directly to the chemical action of the drugs when the latter were taken orally. For example, Terzian (1954) stated that the use of chlorpromazine in clinical doses by mouth did not result in any change in the scalp EEG pattern beyond those associated with changes in vigilance. Dennison and his associates (1955) reported that patients on long term medication with reserpine, one milligram a day, did not show any significant changes of the alpha frequency, response to hyperventilation or to photic stimulation.

On the other hand, a few workers have noted some changes in the cortical rhythms following the administration of the tranquillizing drugs. Liberson (1955) reported on nine patients who had been on oral chlorpromazine up to 400 mg. daily, for five months. He found that those who had a low alpha continuity showed an increase in that continuity and a slight decrease in alpha frequency. The results of parenteral administration of chlorpromazine have also been contradictory. For example, Monroe *et al.* (1955) did not find significant scalp EEG changes with either chlorpromazine (Thorazine) or reserpine, even when given intravenously. On the other hand Bente and Itil (1954), Denber and Merlis (1956), and M. Turner *et al.* (1956) have reported that parenteral injection of chlorpromazine has increased abnormal brain-wave potentials if these were present before the drug was administered.

BENACTYZINE (SUAVITIL, PARASAN) [2]

Benactyzine is one of the newer ataraxic drugs. It is the hydrochloride of benzilic acid diethylaminoethylester. Benactyzine is described as having a central blocking action possibly in the brain stem, and a peculiar clinical reaction in which external reality is divorced from emotional reactions.

The EEG effects of Benactyzine, if any, have not been studied extensively, especially when the drug is given orally.

Raymond and Lucas (1956) gave 5 mg. of Benactyzine subcutaneously to 10 non-patient volunteers and found significant EEG changes in half of the cases. The changes consisted of an increase in muscle artifact, a decrease in the amount, and to a lesser extent in the voltage, of alpha rhythm, and some slowing. They believed that these changes were not specific for the drug but that they represented increased attentiveness on the part of the subjects to altered sensory perceptions, especially to those impulses from the muscles and tendons (propioceptive impulses).

A blocking or suppression of the alpha rhythm has also been reported following the administration of Benactyzine by Coady and Jewesbery (1956) and by Jacobsen (1955). It may be presumed, although it is not stated, that the findings of these workers may be on the same basis as that hypothesized by Raymond and Lucas (1956), although an editorial writer in the Danish Medical Bulletin thought that the EEG effect might be specific for the drug.

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1 The opinions expressed herein are those of the author and do not necessarily reflect the viewpoints or policies of the Veterans Administration.

2 The Benactyzine used in this research was made available to the hospital by the Lloyd, Dabney & Westerfield, Inc., Co. of Cincinnati, Ohio.

MATERIAL AND METHODS

Nineteen patients in a psychiatric hospital were given Benactyzine orally over a 12 week period, beginning with 1 mg. 3 times a day and increasing the dose to 15 mg. 3 times a day. Fifteen of the patients were chronic schizophrenics in partial remission, 2 carried diagnoses of chronic brain syndrome, one was called a passive aggressive reaction type and one was a manic depressive psychotic patient who was in remission.

Control EEG's were taken before the medication was started, again at the end of 4 or 5 weeks when the patients had been on relatively small doses of 3 or 4 mg. and with little clinical effect; still later at the end of 10 to 11 weeks; after the patients had been on 15 mg. doses and when some of them had had tracing was being made and at intervals for one hour thereafter.

Ten lead monopolar recordings with 8 active placements were made, using a Grass Model III 8 channel electroencephalograph with the patients in the supine position.

The tracings were subjected to visual analysis with especial attention to the alpha rhythm and to evidences of mental preoccupation and tension.

Premedication tracings. These consisted of 13 records that were read as normal, 4 that were read as borderline normal because of high alpha incidence and continuity, and 2 that were definitely abnormal due to bilateral slowing. Each record was studied with attention to the frequency and voltage of the alpha rhythm, its incidence and continuity, and the response to eye opening and closing.

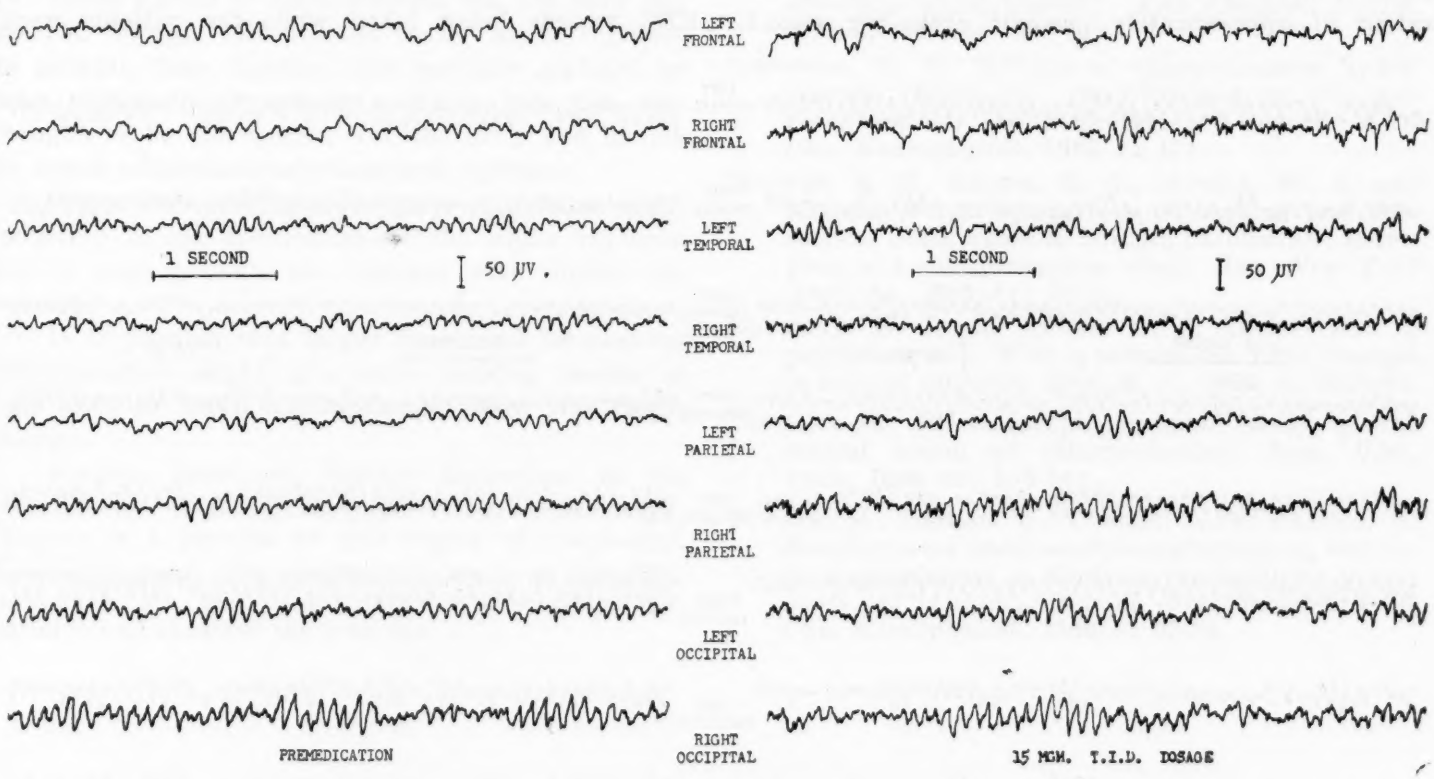

Fig. 1

Type of monopolar scalp recording found in 8 of 19 patients who were receiving 15 mg. of Benactyzine three times a day.

the supposedly typical subjective reactions. However, other of the patients who were on the same dosage claimed to have no subjective effects. It is anticipated that follow-up tracings will be made later after the administration of the drug has been discontinued.

There is evidence that Benactyzine changes rapidly in the body, and in view of this possibility some tracings were made at the time of the administration of the drug while others were run without respect to the theoretical blood level of the Benactyzine. In addition, a volunteer non-patient subject was given the drug in a dose of 10 mg. by mouth while a

Medication tracings.

On smaller doses (3-4 mg. three times a day). There were no significant changes in these records in terms of the criteria mentioned above. Two patients showed evidence of increased attentiveness and tension — less alpha activity and disorganization of the tracing by muscle artifact.

On larger doses (15 mg. three times a day). The changes in the appearance of the alpha rhythms were not uniform. Eight of the 19 patients became more tense and their records showed an increased amount of muscle artifact with breaks in the continuity of

the alpha rhythm, a decrease in amount of alpha in a given time unit, a loss of uniformity or regulation, and a slight increase in alpha voltage (fig. 1). These changes appeared to be those expected from patients who were giving attention to unpleasant body feelings, and there is no reason to think they were a specific reaction to Benactyzine. This same type of record was seen in these patients who were given 15 mg. of the Benactyzine at the time of their tracing and also in the volunteer non-patient subject who took 10 mg. and then complained of a ''scary feeling'' and of the sensory impression that his limbs were detached.

In 8 other patients these tension and attention phenomena were not seen. In 5 cases there appeared to be a slight increase in the voltage but little or no decrease in the incidence or frequency (fig. 2). Only one patient showed any consistent reduction of alpha frequency in all leads and this was to the extent of approximately one-half cycle per second.

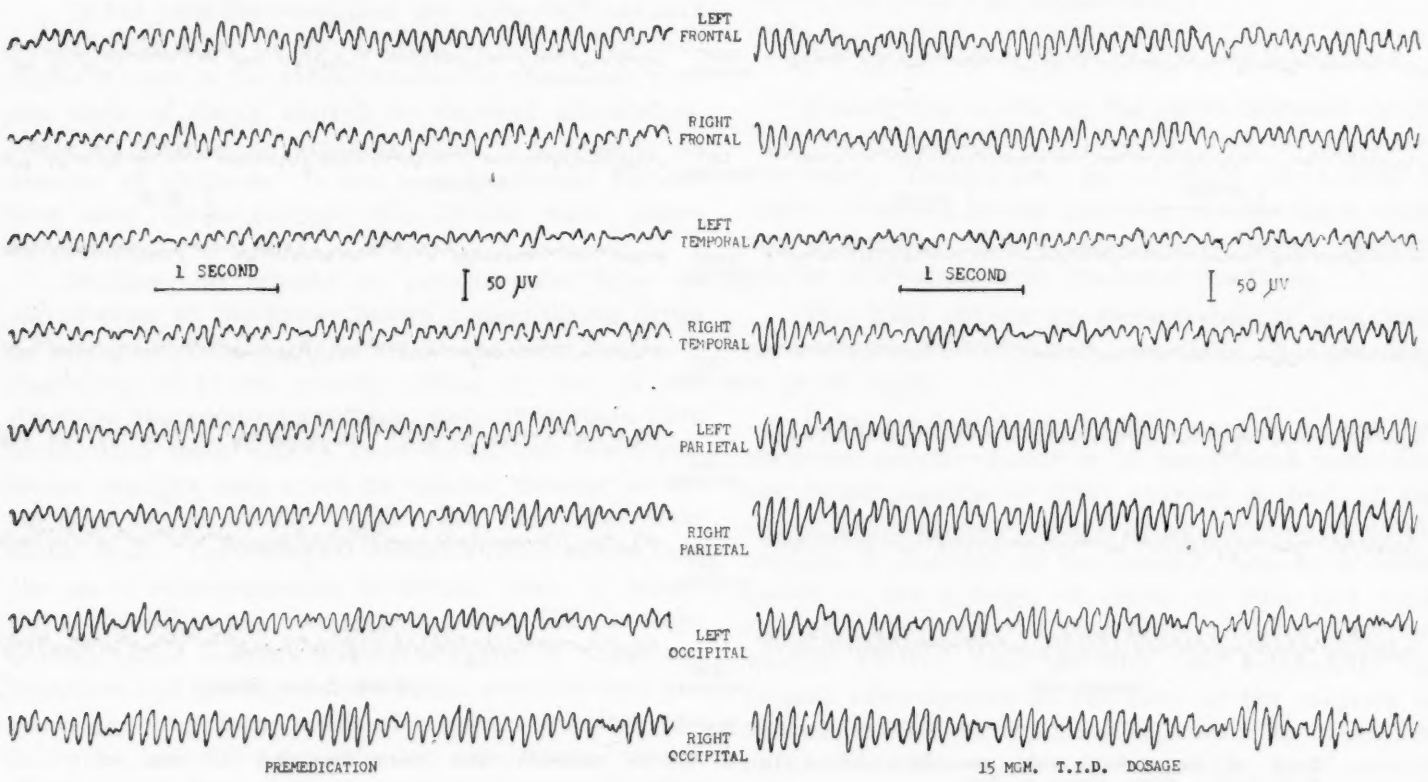

Fig. 2

Type of monopolar scalp recording found in 8 other of the 19 patients who were receiving 15 mg. of Benactyzine three times a day. Clinically, these patients were not appreciably different from the patients who had recordings of the type shown in figure 1.

In contrast, 2 patients appeared to show a slight increase in alpha frequency.

In the 2 patients whose premedication records were abnormal because of bilateral slowing, there was no detectable increase in the amount of slowing after medication.

Only 4 of the patients claimed to be drowsy after taking larger doses of the medication. The more communicative patients and the non-patient volunteer described the subjective experience as a tranquil state rather than drowsiness, but with a fearful feeling because of the loss of feeling of the limbs, and also because of the awareness of a lack of mental capacity based upon poor memory and an inability to sustain interest.

DISCUSSION

The results of this study have not been striking. The records did now show any changes in the alpha rhythm which, by visual analysis, could be related directly to the oral intake of the Benactyzine with the possible but uncertain exception of slight slowing of the alpha frequencies, in about a third of the patients. This was true, regardless of whether the subjects claimed subjective effects or not.

These observations have been limited to patients who were given Benactyzine by mouth with scalp EEG records being taken while the patients were recumbent. While it would appear that the same type of results might follow from appropriate amounts of the drug by oral and parenteral routes, it would be expected that more immediate and more striking results would come about when the drug was taken parenterally. Also, it was common for these patients to have much more marked subjective complaints when sitting up or standing up and a few brief observations showed that there was slowing of the cerebral rhythms

at those times. This slowing was apparently on a hypostatic vascular basis.

Patients who initially had a high incidence of alpha rhythm maintained that incidence while those who had a low alpha incidence continued with that pattern.

The four who became drowsy clinically showed the EEG changes associated with drowsiness, and, in one case, the rhythms characteristic of very light normal sleep.

SUMMARY

Nineteen patients in a psychiatric hospital were given oral doses of Benactyzine ranging from 1 mg. to 15 mg. three times a day. Clinically, some claimed no subjective effects, while others reported a loss of sensations in the limbs and a feeling of apprehension.

Scalp EEG's of these patients did not show any specific changes with respect to the alpha rhythms. In general, those rhythms were partially replaced by beta rhythms and muscle artifact, but this was thought to be non-specific for the drug and merely an aspect of increased alertness and vigilance.

There were occasional instances of possible slight reduction in the frequencies of the alpha rhythms, and in most patients the voltages were slightly increased.

It is possible that larger doses and intravenous administration might give more striking results or that basal or depth tracings might show significant changes.

Finally, there are distinct limitations to the effectiveness of visual analysis of the electroencephalogram in a problem of this degree of complexity.

Acknowledgment with gratitude is made to the EEG technician, Mr. Marvin McConkey, who scheduled the patients and obtained the tracings.

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A NOTE ON PLACIDYL AS A SOPORIFIC IN EEG [1]

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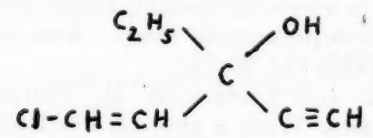
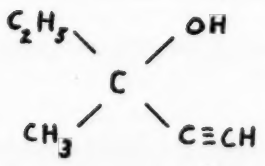
The evaluation of a sleep producing drug for use in electroencephalography involves the following considerations: (1) the rapidity and per cent effectiveness in inducing sleep in a routine patient population referred for EEG study; (2) the relative lack of distortion of normal sleep state patterns; (3) the relative percentage of EEG abnormalities seen in sleep; (4) the toxicity of the drug, and (5) the subjective reactions on arousal.

Placidyl,[2] a non-barbiturate sedative drug introduced to the profession in 1955, seemed from the brochures ideally suited for the induction of sleep



ETHCHLORVYNOL — PLACIDYL



METHYL PARAFYNOL — DORMISON

Fig. 1

for electroencephalographic examination (P'an *et al.* 1955; Toman *et al.* 1956); it was reported to be nontoxic, rapid acting, and to have no after effects. The drug is identified as ethchlorvynol, a designation quite different from methyl-parafynol, the chemical known as Dormison, but as can be seen in figure 1 the two are closely related — a chlorovinyl is substituted for a methyl radical.

Placidyl, in doses of 750 mg. for adults and 250 to 500 for children, was given to 100 in-patients at the Graduate Hospital who were referred for EEG study. The diagnostic breakdown of these patients was similar to a larger group of 1,000 patients studied previously during Dormison or Dormison-Seconal induced sleep (Silverman 1956) and the classification of EEG records in the two groups was also similar, making them comparable groups (table I).

TABLE I
DIAGNOSTIC CATEGORIES

	Placidyl	Dormison
Epilepsy	25	300
Functional	21	211
Vascular	12	119
Tumor and B.T.S.	11	136
Trauma	12	99
Degenerative	9	49
Miscellaneous	10	86
	100	1000

EEG CLASSIFICATION

Normal	52	448
Minimal	9	113
Non-focal	14	173
Focal	25	266
	100	1000

Satisfactory sleep or drowsy state recordings were obtained in 76 per cent of patients with Placidyl, a figure comparable to that obtained with Dormison. The earliest occurrence of sleep was within 5 min. after the administration of the drug and the latest 60 min. (if no sleep was obtained by then Seconal was given); the average time was 26 min. This again was comparable to the Dormison study. The quality of the sleep state EEG was judged to be equivalent to natural or Dormison induced sleep or drowsiness in 47, to be slightly faster than natural or Dormison

1 Presented at the March 1957 meeting of the Eastern Association of Electroencephalographers.

2 Placidyl was supplied by the Abbott Laboratories, North Chicago, Ill.

induced sleep in 12 and distinctly faster in 17 (fig. 2). At times in the latter group, when the patient was awakened, there was exaggeration of the beta components in the resting record. Twenty patients had previous or subsequent records with either natural, Dormison or Dormison-Seconal induced sleep. These sleep showed that these were of the same general character and quantity as those obtained through Dormison induced sleep (table II). The value of the sleep state record, as judged by whether the abnormalities were significant (i.e., did not occur at all in the remainder of the record or only suggestively

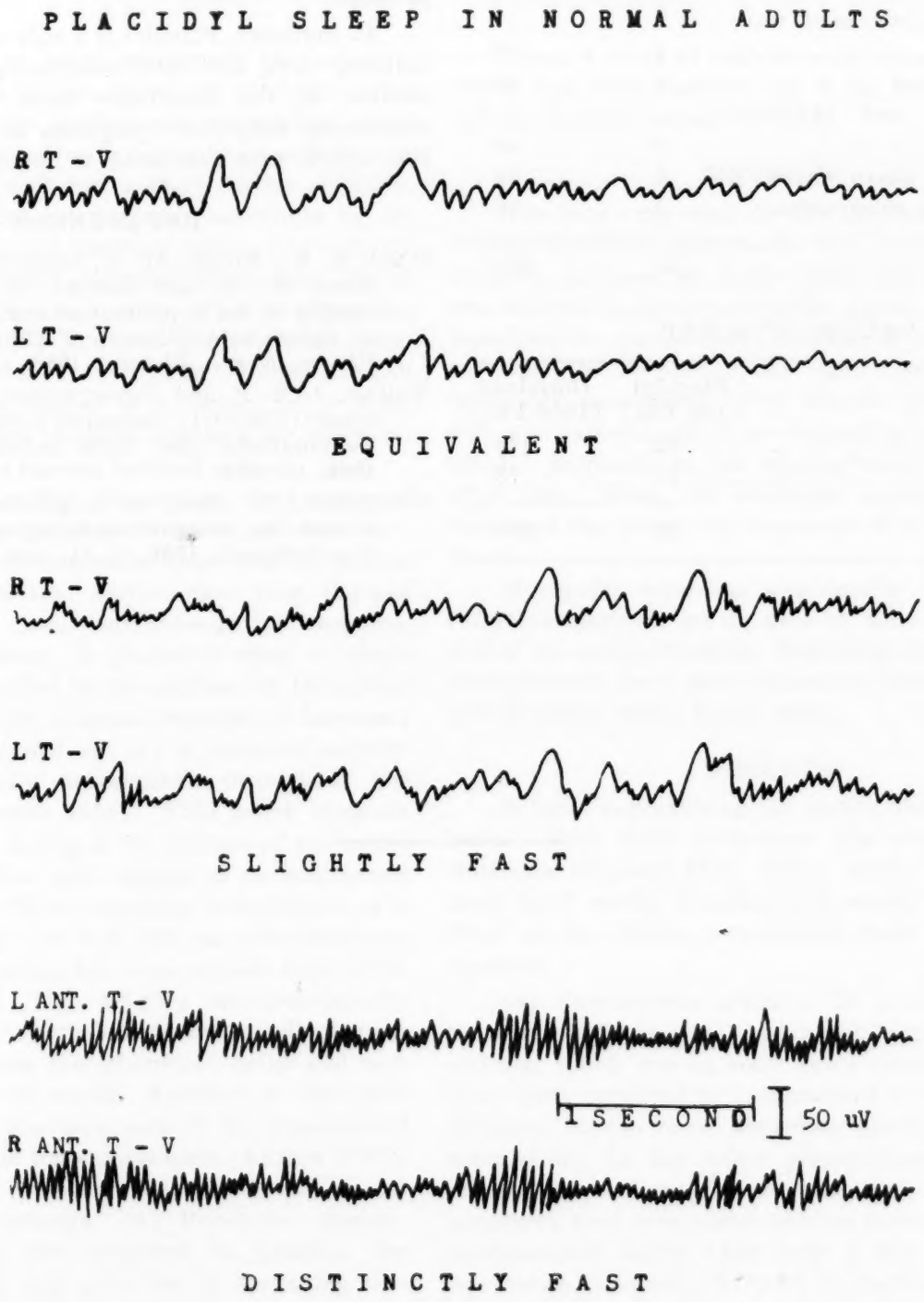


Fig. 2

offered some direct comparisons and substantiated the impression that Placidyl gave distinctly less potentiation of the fast components than Seconal, but more than Dormison or natural sleep.

Study of the types of abnormalities revealed in so) or contributory (i.e., confirmed what appeared in the remainder of the record), compared favorably to the Dormison induced sleep study (table II).

There were no serious toxic effects that could be attributed directly to Placidyl. One patient was dif-

TABLE II

TYPES OF SLEEP ABNORMALITIES

	Placidyl (100 Pts.)	Dormison (1000 Pts.)
Generalized spike-waves	2	29
Gen'l. random and rhythmic spikes	4	35
Other Gen'l. paroxysmal wave forms	1	6
Focal spike-waves	2	33
Focal random and rhythmic spikes	5	43
Focal slow and sharp waves	6	39
Focal slow with suppression	2	16
	22	201

VALUE OF SLEEP

	Placidyl (100 Pts.)	Dormison (1000 Pts.)
Contributory	12	123
Significant	10	78
	22	201

ficult to rouse, and 9 other patients upon arousal at the completion of their EEG's complained of excessive and distressing sleepiness, grogginess and dizziness, a feeling akin to alcoholic intoxication; 6 of these patients had increased fast activity in their EEG's. Less disturbing complaints of "light-headedness" and some drowsiness were encountered in another 12 patients.

In summary, Placidyl is a safe and effective sleep inducing drug for electroencephalography. However, because of the occurrence upon early arousal of distressing subjective symptoms in some individuals Placidyl is best restricted to in-patient usage.

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SOME PRELIMINARY ELECTROPHYSIOLOGICAL STUDIES ON CHRONIC NEURONALLY ISOLATED CEREBRAL CORTEX

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It is possible to sever completely the neuronal connections from a given region of cerebral cortex to the adjacent grey matter and underlying white matter, without destroying its pial blood supply. In such an isolated area of cortex shortly after isolation, spontaneous electrical activity may sometimes be observed (Kristiansen and Courtois 1949), and activity may be elicited by direct electrical stimulation (Burns 1950, 1951). Even several months after isolation, the isolated tissue may still be viable and electrical activity may be recorded from it (Echlin, Arnett and Zoll 1952). The present paper is a report of a brief survey which has been made to compare the electrical activity of acute and chronic isolated cortex.

As the basis for this comparison, four types of cortical responses to direct electrical stimulation have been examined. These responses, which may be elicited from the unanaesthetized cortex, have been defined as follows: (1) A local surface-negative response, lasting about 20 msec., is produced when a single weak stimulus is applied to the surface of the cortex (Burns 1950). If the stimulus strength is increased this response is followed by (2) a burst of activity which is synaptically transmitted throughout the isolated region (Burns 1951). This burst response lasts 0.5-2 sec., and during it the surface of the active tissue becomes positive with respect to an indifferent cortical point. (3) With repetitive stimulation at a rate of 5-10 per sec. for 5-10 sec. an afterdischarge may be produced, lasting for some seconds after stimulation has ceased. This activity characteristically consists of a train of brief, high voltage discharges, which spread out from the stimulated point and may involve large areas of cortex. Activity of this kind in the motor cortex has been seen to be accompanied by epileptiform clonic limb movements (Adrian 1936), and this response is therefore referred to as an epileptiform afterdischarge. (4) Repetitive stimulation stronger than that required to produce the epileptiform activity may give rise to spreading cortical depression (Leão 1944). This response is readily detectable even in those preparations of isolated cortex which are not spontaneously active, since it is accompanied by a slow negative shift of the potential of the cortical surface (Grafstein 1956).

These 4 types of activity were examined in cortex which had been isolated for 2 to 8 weeks, and in acutely isolated cortex.

METHODS

Ten cats were used for the chronic preparations. Under Nembutal anaesthesia and with aseptic precautions, an area of cortex about 0.5 cm. × 2 cm. was isolated in the suprasylvian gyrus, in the manner described by Burns (1951). After 2 to 8 weeks the cat was decerebrated under ether anaesthesia, then taken off anaesthetic. The chronic isolated cortical slab was exposed, and a corresponding acute slab was usually prepared in the suprasylvian gyrus on the other side. When the electrical activity was to be examined the cortex was immersed in a pool of paraffin oil.

Monopolar recording was usually used, with the reference electrode on an area of dead cortex at one end of the isolated region. Recording and stimulating arrangements have been described elsewhere (Burns and Grafstein 1952; Burns 1954).

RESULTS

A table summarizing the results obtained is given below. Very little difference was observed in the responses obtained from cortex which had been isolated for 2 weeks, 4 weeks, or 8 weeks, so the results from all the chronic preparations have been included together.

(*a*) *Spontaneous activity.* In 9 out of 10 cats the chronically isolated cortex exhibited spontaneous activity, which was in some cases continuous, but in most cases consisted of intermittent bursts similar in character to the burst responses produced by direct stimulation. In the acute preparations spontaneous activity was not usually observed, but Burns (1954) has shown that even silent isolated cortex may become spontaneously active after only a few stimuli. For this reason it is very difficult to decide whether this difference between the acute and chronic preparations represents a significant alteration in the properties of the cortex.

(*b*) *Surface-negative response.* Although the threshold stimulus for eliciting this response was considerably higher in the chronic preparations, the distance over which the response could be recorded

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was not significantly different in the two kinds of preparations.

(*c*) *Burst response.* The threshold for this response did not change as a result of the chronic isolation, but the amplitude of its surface-positive "D.C." component was apparently reduced to some extent, the difference between the responses in the acute and chronic preparations being statistically significant at a 5 per cent level of confidence. In two chronic preparations it was observed that in each burst an initial brief surface-negative phase preceded the onset of the surface-positive potential.

very much higher. In 5 out of 8 chronic preparations tested depression was not produced by repetitive stimulation in the range of strengths tested (see footnote to table I), and surface-negative polarization with currents of up to 2000 μA. was also ineffective. Even in these cases, however, as in the acute preparations, depression could be initiated by mechanical stimulation or by the topical application of 1 per cent KCl.

COMMENT

After 2 to 8 weeks the neuronally isolated cerebral cortex showed relatively little alteration in its electro-

TABLE I

	Acute	Chronic	P
Threshold for surface-negative response with 1.2 msec. stimulus (V.).	1.5 ± 0.4 (5)	2.9 ± 0.4 (7)	< 0.001
Distance over which surface-negative response may be recorded (mm.).	9.8 ± 0.4 (2)	7.8 ± 0.6 (5)	0.3 — 0.2
Threshold for burst response with 1.2 msec. stimulus (V.).	2.7 ± 0.6 (7)	3.0 ± 0.5 (7)	0.8
Amplitude of surface-positive component of burst (μV.).	193 ± 80 (4)	95 ± 29 (5)	0.05
Threshold for epileptiform afterdischarge (40 stimuli, 8/sec. 1.2 msec.) (V.).	11.0 ± 4.9 (5)	6.1 ± 1.6 (7)	0.05 — 0.02
Duration of epileptiform afterdischarge at threshold stimulus (sec.).	7.4 ± 6.6 (7)	64 ± 35 (6)	0.001
Threshold for spreading depression (stimuli 1.2 msec. at 10/sec. for 10 sec.) (V.).	11.3 ± 3.8 (6)	> 17.0 * (8)	—
Amplitude of slow negative potential during depression (mV.).	8.0 ± 3.2 (5)	2.5 ± 1.2 (7)	0.02 — 0.01
Rate of spread of depression (mm./min.).	4.5 ± 1.5 (3)	3.6 ± 1.2 (8)	0.4 — 0.3

* In 5 out of 8 cats depression was not produced with the strongest stimuli tested, which ranged between 15 and 25 V.

Comparison of some properties of acute and chronic neuronally isolated cerebral cortex. In each case the mean and its standard deviation are given, the number of preparations from which the results were drawn being stated in parentheses. P = probability that the two sets of results are not significantly different.

(*d*) *Epileptiform afterdischarge.* A lowered threshold and considerably prolonged duration were characteristic of this response in the chronic preparations.

(*e*) *Spreading depression.* When depression was initiated in the chronic isolated cortex, its rate of spread was comparable to that in the acute preparations. However, the amplitude of the accompanying slow potential change was smaller, and the threshold for depression, tested with repetitive stimulation, was

physiological properties. All of the responses which were produced by electrical stimulation in the acute preparation could also be elicited in the chronic one, although there were some changes in the thresholds and amplitudes of the various responses. Possibly the most interesting feature of the electrical behaviour of the chronic isolated cortex was the long duration of the epileptiform afterdischarge which could be produced in it. In cortex which has been isolated for longer periods than those in this study, this after-

discharge has been found to be even more prolonged. For example, in cortex isolated for 6 months, an after-discharge could be initiated which lasted for several hours (Burns and Sastry, unpublished results).

It is not possible, on the basis of this brief survey, to make any speculations on the nature of the structural changes underlying the observed changes in the electrophysiological properties of the isolated cortex. We hope, however, that these preliminary observations will be of use in the further exploration of this problem.

Our thanks are due to Professor B. D. Burns for his valuable advice, to Professor F. C. MacIntosh for his interest in this study and to Mr. Carl Holizek for his assistance in the aseptic operations. One of us (Sastry) wishes to express his thanks to the Technical Co-operation Service of the Canadian Government for the award of the fellowship under the Colombo Plan. This research was supported by a grant to Professor Burns from the National Research Council of Canada.

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VARIATION WITH ELECTRODE SIZE OF THRESHOLDS FOR MOTOR RESPONSES TO CORTICAL STIMULATION

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There have been numerous studies of the effects of altering stimulus parameters on responses to repetitive stimulation of the motor cortex. For example, Lilly, Austin and Chambers (1952) studied variations in threshold with pulse duration and frequency, using rectangular current pulses. More recently, Cure and Rasmussen (1954), using *Macaca Mulatta*, studied the effects of various waveforms and frequencies, not only on the voltage threshold but also on the type of motor response obtained. These papers together review adequately the earlier literature.

One stimulation parameter which has received little or no attention is the area of contact between the stimulating electrode and the cortex. The experiments to be described here were carried out to determine the effect of variation of this parameter on the voltage and current required to elicit motor responses. In particular, it was desired to find out if either voltage or current threshold were independent of variations in electrode contact area.

METHODS

Adult cats were used in all experiments and were anaesthetized with about 80 mg/kg. Dial given intraperitoneally. Light surgical anaesthesia was maintained by additional injections when required. The head of the animal was mounted in a stereotaxic instrument and the left sensory-motor cortex exposed. The skin around the opening was sewn up to a metal ring and the cavity filled with liquid paraffin.

Stimulation was monopolar, the indifferent electrode being a large metal screw in the skull. There was no indication of polarization or fluctuating impedance at this electrode. Each stimulating electrode consisted of a column of agar gel, made up with 10 per cent NaCl solution, in which was imbedded a coil of chlorided silver wire. The gel was contained in a glass tube (fig. 1). Contact with the cortex was made through a pore in a nylon plug fitted into the end of the tube. The 7 electrodes used were identical except for the cross-sectional area of the pore, which ranged from 0.25 to 5.0 mm.^{2}. They were lowered individually into identical positions on the cortex by means of an electrode carrier attached to the stereotaxic instrument.

Positive rectangular pulses of 6 msec. duration were applied to the stimulating electrode at a frequency of 80/sec. Stimulus duration was 2 sec. Two minutes were allowed between stimuli to avoid cumulative effects of repeated stimulation. The stimulating voltage and current were both monitored on a two-channel oscilloscope.

One of the electrodes was placed on the motor cortex and its position adjusted until a point of minimum threshold for a suitable movement was located. Movements selected (for example flexion or extension of the knee or ankle in the contralateral front or hind limb, or abduction of the shoulder or hip) were well defined and unequivocally reproducible.

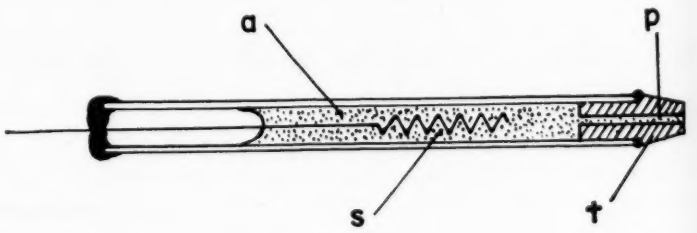

Fig. 1

Longitudinal section of stimulating electrode. The glass tube is filled with agar gel (a) made with 10 per cent NaCl solution. Stimulator is connected to chlorided silver spiral (s) imbedded in the gel. Nylon tip (t) and lead to stimulator are sealed to the glass with deKhotinsky cement. The 7 electrodes used were identical except for the diameter of the pore (p) in the tip.

The threshold voltage and current were then measured with the first electrode and each of the other six, and the results plotted as illustrated in figure 2. Several measurements were made with each electrode at each cortical point.

RESULTS

Movements were obtained from both the anterior and posterior sigmoid gyri. In figure 2 the threshold voltage and current required to produce knee flexion in the hind limb were plotted against the cross-sectional area of the stimulating electrode. The regression line plotted for the current values has a slope which is not significantly different from zero. That is, the threshold current was independent of electrode

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area in the experimental range. The threshold voltages fall close to the theoretical curve $V = V_1 + V_2/A$, where A is the electrode area. V_1 may be taken to represent the voltage dissipated across the combined resistances of the brain, skull, indifferent electrode contact and the AgCl — agar junction. These resistances are independent of electrode area. Consequently if the threshold current is constant with varying area then V_1 will be constant also. Again assuming constant current, V_2/A represents the voltage dissipated in the electrode tip, V_2 being constant and equal to the voltage drop in the tip of unit cross-sectional area.

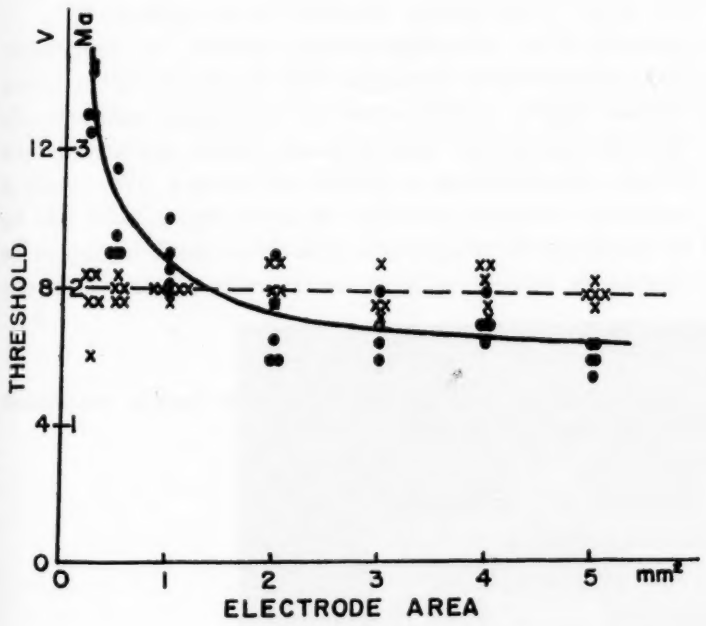

Fig. 2

Relation between thresholds and electrode size. Abscissa: cross-sectional area of stimulating electrode. Ordinate: stimulating current and voltage. X: threshold current for knee flexion in response to stimulation of the anterior sigmoid gyrus. Dashed line is the regression line fitted to these points. ●: Threshold for same movement expressed in terms of voltage applied to the electrode. Solid line is theoretical curve $V = V_1 + V_2/A$, fitted to the experimental points, where V is the threshold voltage, V_1 and V_2 are constants and A is the electrode area (see text).

These results are typical of those obtained from a total of 9 cortical points in 5 animals, except for one point where there was a slight but significant increase in threshold current with increasing electrode area. The amount of current required to elicit motor responses was not only relatively independent of electrode area but showed remarkably small variation from experiment to experiment. Its value always lay in the range 2.0 to 3.5 mA.

During one experiment the stimulus frequency was altered to 120/sec. and the pulse width to 4.0 msec. These alterations had no effect on the relation between electrode size and threshold voltage and current.

DISCUSSION

The results obtained here indicate that under conditions where electrode contact areas are unknown or variable, current measurements would be expected to provide a more reproducible indication of thresholds for excitation than would voltage measurements. However, with agar electrodes the threshold voltages also become relatively independent of the electrode area if this area is greater than about 3 mm². A few preliminary experiments indicated that this was also true of silver electrodes.

If the motor responses were initiated by the activity of a few cells immediately under the stimulating electrode, an increase in threshold current might be expected as the electrode area was increased. That is, some of the current from the larger electrodes would be expected to pass outside the volume occupied by the cells concerned in the movement, and so not contribute to their excitation. The fact that there is no significant increase in threshold current with the largest electrode area used (5 mm.²) indicates that the cortical area involved in the discrete movements observed is at least this great. This is in agreement with the results of Phillips (1956) who found that single shocks at a strength just adequate to produce flick movements resulted in the excitation of pyramidal cells over a minimum radius of 4 mm. from the stimulating electrode. On the other hand Ward and Clark (1935) and Lilly *et al.* (1952) report different motor responses in the cat from cortical points as little as 3 mm. apart. Perhaps, as suggested by Liddell and Phillips (1952), the selective elicitation of a specific movement is due largely to the group of cells subserving this movement being in the majority of those stimulated.

SUMMARY

1. The motor cortex of cats was stimulated with electrodes ranging in cross-sectional area from 0.25 to 5.0 mm.².

2. Within this range, the minimum current required to elicit movements was found to be independent of the contact area between the stimulating electrode and the cortex. The voltage applied to the stimulating electrode at threshold increased as the electrode size decreased.

3. Because the threshold current is independent of electrode area up to an area of 5.0 mm.², it is concluded that the cortical area involved in the production of discrete movements is at least this great.

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ANNOUNCEMENT

THE AMERICAN PSYCHIATRIC ASSOCIATION
THE HOFHEIMER PRIZE

The Hofheimer Prize of $1,500 is awarded annually by the American Psychiatric Association for an outstanding research contribution in the field of psychiatry or mental hygiene which has been published within three years of the date of the award. The competition is open to citizens of the United States and Canada not over forty years of age at the time the article was submitted for publication; or to a group whose median ages do not exceed forty years of age. The next award will be made at the Annual Meeting of the Association in May 1958. Articles submitted to the Prize Board before March 1, 1958 will be considered. Eight copies of each publication and data concerning age and citizenship should be sent to John I. Nurnberger, M.D., Chairman, Hofheimer Prize Board, 1100 W. Michigan St., Indianapolis 7, Indiana.

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TECHNICAL NOTES

Editor for Western Hemisphere and Far East, J. KNOTT, Iowa City, Iowa, U.S.A.
Editor for Europe and Middle East, H. SHIPTON, Bristol, England

THE SIMULTANEOUS PHOTOGRAPHIC RECORDING OF SEVERAL OSCILLOSCOPE GUNS [1]

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Department of Anatomy, The Creighton University School of Medicine, Omaha, Nebraska

(Received for publication: June 9, 1957)

Difficulties were initially encountered when we attempted to record photographically and simultaneously the traces of four separate oscilloscopes. Obviously this could not be done with a single oscillorecord camera which covered only one scope face at a time. We wanted to obtain a simultaneous record of the four scope faces in order to compare latencies of response from various brain regions responding to the single shock stimulation of a particular structure. varying characteristics of successive responses, and permitting more detailed study of latency and spread.

The oscilloscope tubes were rather easily mounted in the fashion illustrated in figure 1. The Automatic Engineering Co. of Omaha, Nebraska, fabricated the master chassis from Unistrut materials and aided us in mounting the equipment so that any unit is easily removed and restored to its original portable condition. Special extension cords were made for the

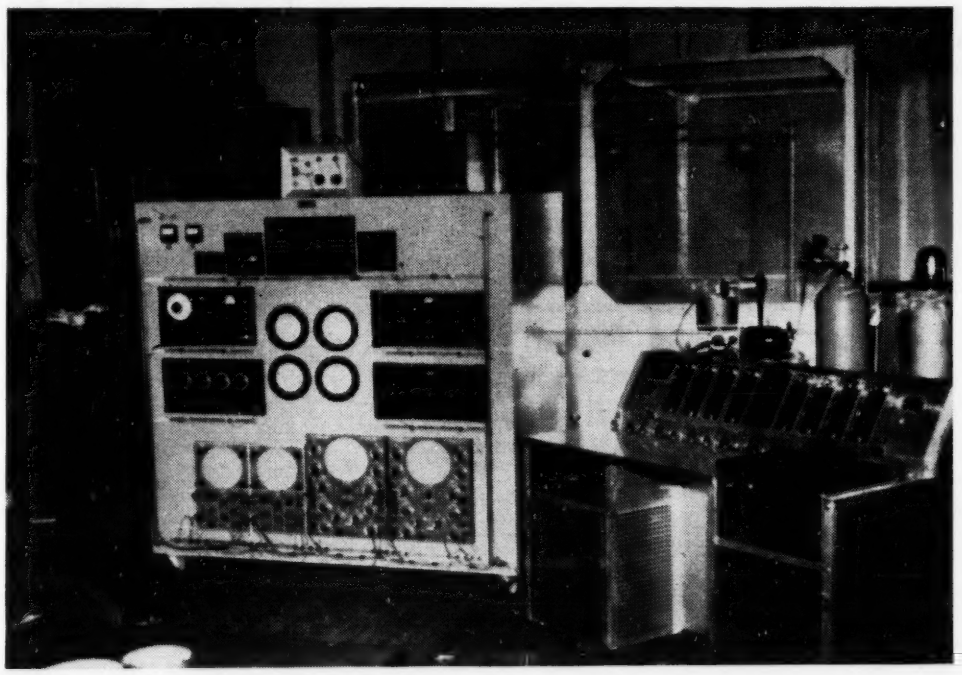

Fig. 1
The arrangement of oscilloscope guns which permits the convenient simultaneous photographic recording of as many as 6 independent traces. Other electronic equipment is also mounted in the master chassis.

Our principal objectives can be summarized as follows: (*a*) to record four oscilloscope faces at a single exposure; (*b*) to procure records having good contrast and of a size scale that permitted immediate mounting on prepared scale drawings of the cat's brain, and (*c*) to record repetitive traces from a single oscilloscope, thus facilitating comparison of oscilloscope guns using Belden 18 AWG stranded hook-up wire and tube bases and sockets (collar bases, split collar sockets, tube bases, and base sockets) purchased from Allen B. DuMont laboratories.

A crown graphic camera with an Optar 135 mm. f 4.7 lens employing the polaroid back proved most suitable for photography. Polapan 400 type 44 film is sufficiently fast and sensitive to record the traces (fig. 2). The camera, as we use it, is simply mounted

1 This work was supported by a grant (B-1046) from the U.S.P.H.S.

on a Husky Quick-set tripod and placed at a distance of about two feet from in front of the tube faces which are then focused on the ground glass, then refocused by using the focusing plate supplied with the polaroid back. The resulting pictures were of the desired scale size so as to permit immediate mounting on scale drawings of the cat's brain. The intensity of the scope screen was so adjusted as to give the contrast shown in figure 2 when the diaphram setting of the camera was f 4.7 with shutter set on bulb. In obtaining the picture shown in figure 2, we did not use a light shield between the scope faces and the camera but merely pulled down the shades in the laboratory and turned out the lights while the picture was being taken. A Grass IIID EEG was used to amplify the signals led to the oscilloscopes by simply tapping (we used equal lengths of shielded coaxial cable) jack 8 (plate) of the 6SL7 amplifier tube.

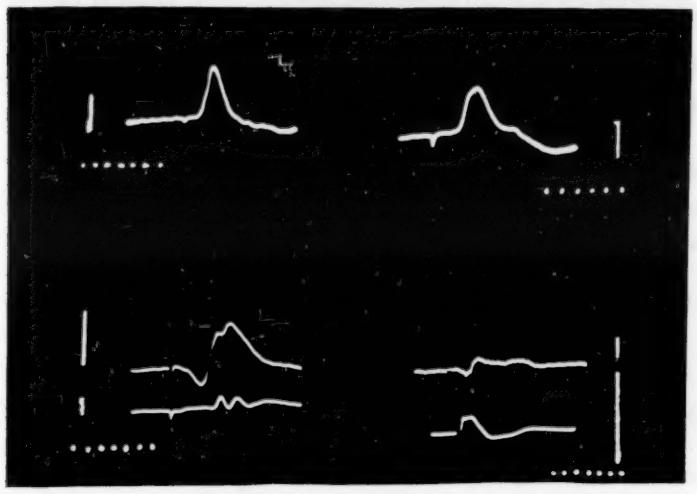

Fig. 2

Traces showing latency of 6 different areas in the cat's brain (upper left, anterior hypothalamus; upper right, middle hypothalamus; lower left, mamillary body and lateral gyrus — posterior inferior part; lower right, septum and amygdala) from stimulation of the ventral hippocampus with 6 V. 0.5/sec. and a pulse duration of 2 msec. The voltage calibration lines represent 100 μV. The time calibration equals 20 msec. between each dot.

Objective (c), recording of repeated traces on the same polaroid frame, has not been fully realized but we are convinced that it is within our grasp. A light shield will be desirable for the scope chosen in order to obtain repeated exposures on the same frame, and in addition it will also be necessary to have some means to determine the exact position of the image of the trace on the film.

If one mounted 6 double beam scopes in such a fashion as we have described, 12 simultaneous traces representing 12 response foci could be photographed.

Reference: NIEMER, W. T. and POWELL, E. W. The simultaneous photographic recording of several oscilloscope guns. *EEG Clin. Neurophysiol.*, **1957**, *9*: 729-730.

PRINTED IN CANADA

TIME LAPSE INDICATOR FOR PEN AND OSCILLOSCOPE RECORDING [1]

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State University of Iowa, Iowa City, Iowa

There is need for a device which can provide an automatic indication of the passage of time on both ink-writer EEG records and cathode ray photographs. Provocative tests such as photic driving and hyperventilation may be more useful when time after the initiation of the test is recorded periodically and automatically. This information is particularly essential in ERG work when following the course of dark adaptation. Lapsed time at any point can be calculated when the paper speed of the recording is known but this requires either continuous paper travel or much clock watching and record notation, subject to the usual errors.

When photographing the oscilloscope on moving film one should be able to correlate pen records with film. The ink tracings may be used for gross estimates of response and for writing special notes about the test conditions. Developed film is usually not available until much later. Automatic numbering of ink and film records makes it simple to locate responses. Simultaneous recording of time has given this information. Since we use moving film, it was not possible to photograph a watch placed beside the CR tube.

The film in our procedure travels for 1.2 sec. at a rate of 5 cm/sec. when recording ERG responses. The paper speed of the ink-writer monitor is 60 mm/sec. We therefore wanted time signals starting with the commencement of dark adaptation and available for recording every second. In order to make lapsed time easily perceived we decided, after much experimentation, to let a sine wave indicate every second, followed by a positive pulse; the delay or time lag between the two would be a function of the number of minutes past zero time. A negative pulse would also follow, its delay being a function of the number of seconds past zero time. These signals would activate both an unused EEG pen, and three glow tubes located at the base of the CR tube.

The ink and CR recordings of time are easily read by placing a ruler, scaled for this purpose, below the time tracings. The bottom lines of figure 1 illustrate the two types of records. The relation of minute (M) and second (S) marks to the reference (R) wave in this drawing would be read on our ruler as 7 min. and 11 sec. past zero time.

The motor, gears, and circuit which produce this signal are housed in a metal box 6 × 8 × 7 inches. A 60 RPM synchronous Bodine motor provides the time base by rotating three cams. These cams activate microswitches which signal neon glow tubes and the pen amplifier through appropriate circuits. Figure 1 is a functional drawing of the mechanics involved. Professor Sutherland, of the University of Iowa Engineering Department, calculated the proper gear ratios and developed a suitable clutch to permit placing all cams in phase (zero time) when desired. The gears were cut from nylon rod by Mr. Walters of our machine shop. The unit is reasonably quiet.

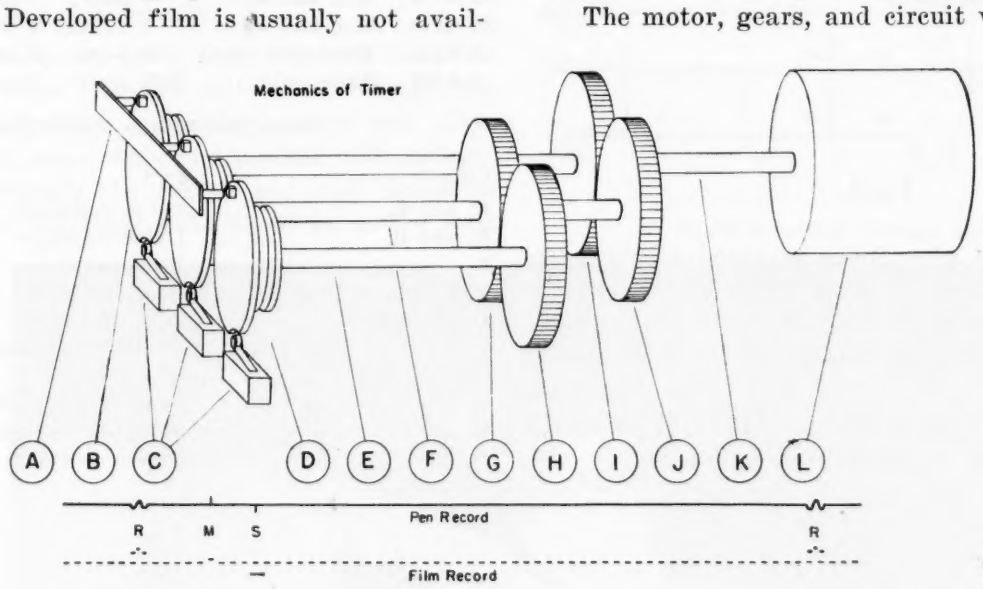

Fig. 1

1 The development of this device was supported by a grant-in-aid from the U.S. Public Health Service awarded to Dr. H. M. Burian, Department of Ophthalmology, College of Medicine, State University of Iowa.

Motor (L) turns the reference shaft (K) one revolution each second. A gear (I) on this shaft has 59 teeth which engage a 60 tooth gear (J). Its shaft (F) rotates in and out of phase with the reference shaft once each minute. This lag produces the lapsed seconds marks. This shaft (F) also has a gear (G) with 61 teeth which engage the fourth gear (H) with 60 teeth mounted on shaft E. It rotates in and out of phase with the reference shaft once each hour. This lag produces the lapsed minute marks. The three cams (B) can be brought in phase by pressing the zero time bar (A). Slippage between each cam and its backing plate is permitted by foam rubber clutches (D). The cams activate the three microswitches (C).

The timer circuit, figure 2, was designed to

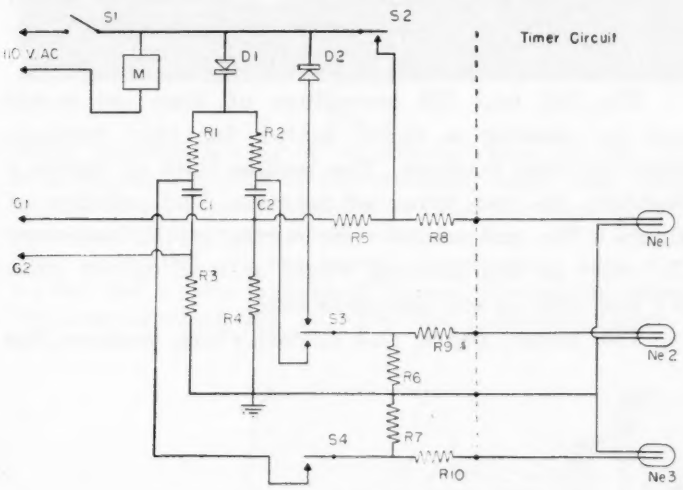

Fig. 2

energize three neon glow tubes mounted at the base of the cathode ray tube. They cover the bottom 2 cm. of the tube. In addition a low voltage signal is provided for input into one channel of the EEG amplifiers.

The switches operate in the following manner. S_2, when closed for a moment each second by the reference cam, connects glow tube Ne_1 and G_1 of the pen amplifier to the AC supply line. When the notch of the minute cam momentarily activates S_3, the rectified AC voltage is removed from the upper electrode of NE_2, and a voltage of opposite polarity is substituted. This condenser discharge signal also appears on G_1 of the pen amplifier. Lastly, the notch of the cam indicating lapsed seconds momentarily closes S_4 which energizes Ne_3 and also causes the pen to deflect downward.

This timer has been in daily use now for over a year without developing any trouble. It has served our purposes very well. It writes its information using a minimum of space and could be readily adapted to other requirements using slower or faster paper or film speed. It could serve as an accumulative time clock totaling up to 5 months or more. If the three microswitches were wired in series it could serve as an alarm clock for distant maintenance checks. The unit we use is equipped with a 60 RPM motor. The table below indicates the parameters when using this and other timer motors.

Timer Motor	Scale Intervals	Total Period	Minimal Recording Speed	Write-out Rate
60 RPM	Min. and sec.	1 hour	5 cm/sec.	1/sec.
30 RPM	Min. and sec.	2 hours	3 cm/sec.	1/2 sec.
1 RPM	Hours and min.	60 hours	5 cm/min.	1/min.
1 RPH	Hours only	3600 hours	5 cm/hour	1/hour

Parts List for the Timer Circuit

Circuit No.	Part
R_1 and R_2	330 K resistors
R_3 and R_4	1 ohm resistors
R_5	150 K resistor
R_6 and R_7	33 K resistors
R_8, R_9 and R_{10}	47 K resistors
C_1 and C_2	1.0 Mfd condensors
Ne_1, 2 and 3	Ne—2 tubes
S_1	SPST toggle switch
S_1, 2 and 3	SPDT micro switches
D_1 and D_2	Sarkes selenium rectifier model 50

Reference: ARNOTT, G. P. Time lapse indicator for pen and oscilloscope recording. *EEG Clin. Neurophysiol.*, **1957**, *9*: 731-732.

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SUCTION CUP ELECTRODES

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(Received for publication: March 20, 1957)

The Burden Neurological Institute was asked to take electroencephalograms of oedematous premature babies at the Bristol Maternity Hospital.

The chief difficulty encountered was the application of the electrodes because the skin of these babies is often particularly delicate. For this reason it was thought that the button type electrodes attached to a rubber band, used by Dreyfus-Brisac, Sampson and Fischgold (1955) and the stocking hat method, described by Harris, Rhodes, Tizard and Walker (1957) were unpractical as they both necessitate too much handling in their application when dealing with oedematous infants. Therefore, a new type of electrode was devised which can be merely placed on the head and held in position by slight suction. No cap or other holder is necessary and no cleaning of the skin by alcohol is required. The five electrodes used are applied within a few seconds.

These electrodes are made from one inch diameter rubber suction cups (window buttons), through the top of which is inserted a chlorided silver rod. This rod is bell-shaped at the base and padded with sponge. Also inserted through the rubber cup and sealed in position is a thin polythene tube about 12 inches long and 1½ mm. in diameter which is connected to a medical vacuum pump by ¼" rubber tubing. Nylon sponge is cut to the shape of the belled silver rod.

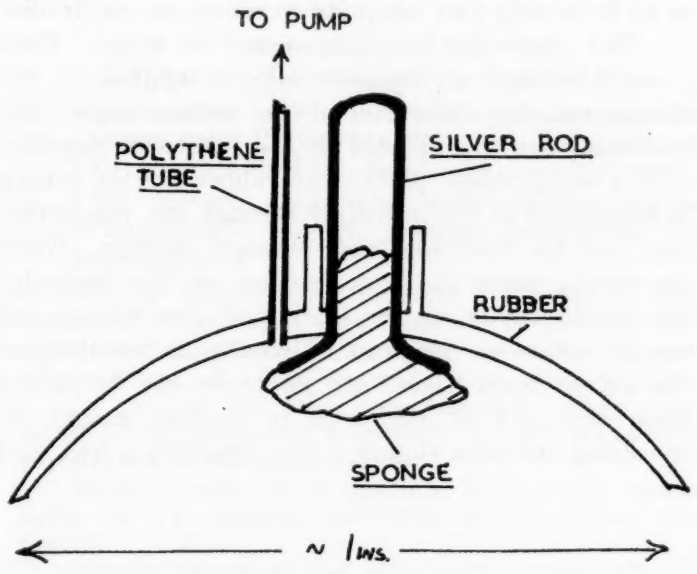

Fig. 1
Shows a section through an electrode.

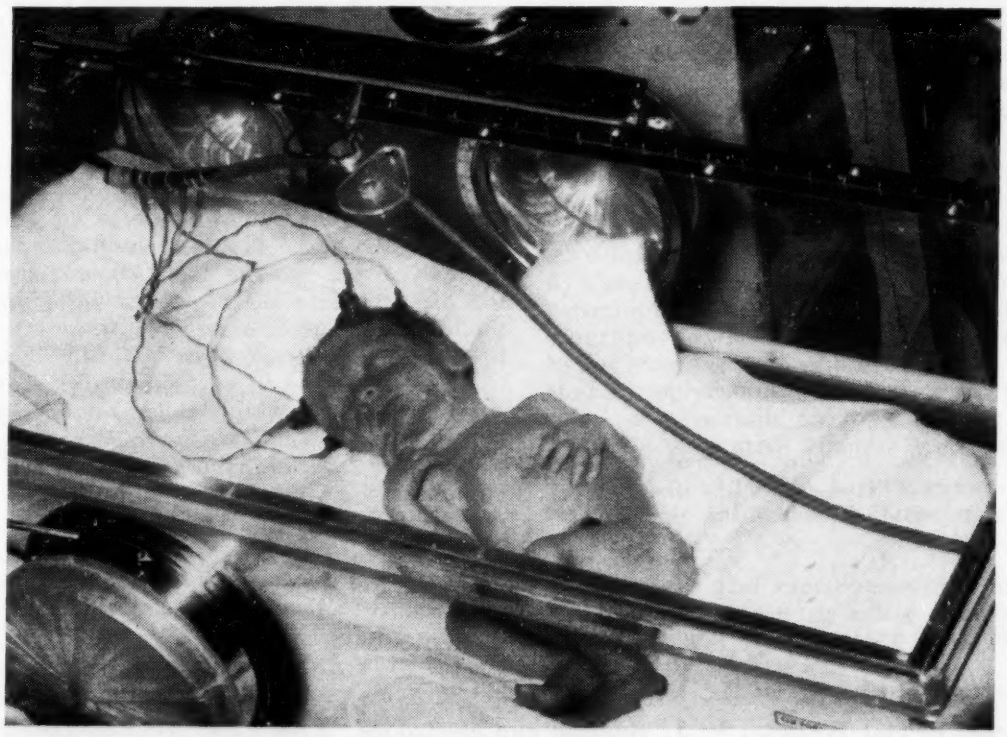

Fig. 2
Electrodes in position on oedematous premature baby in incubator. Suction tube passing out to right of incubator through ventilation hole, electrode lead passing to left.

This was used in preference to natural sponge as it keeps its shape when wet and does not shred, thus avoiding the risk of blocking the polythene tube. Figure 1 shows a section through an electrode. Small leaks due to irregularities of the surface or hair on the head are well within the capacity of the pump and in fact any 2 of the 5 electrodes used need not be in contact with the head at all, the polythene tubing presenting a high "impedance". The force holding the electrode down is easily adjusted by a controlled leak so as to be only just adequate to retain the electrodes.

The electrodes are first soaked in saline. Then a small amount of electrode jelly is applied to the sponge and the outer rim of the rubber cups. The electrodes are then placed in the incubator together with a small plastic plate. The rubber suction tubing is passed out of the incubator through one ventilation hole and the electrode leads through another. When the suction pump has been switched on, the electrodes are placed firstly on the plate and then transferred one at a time to the head. Virtually no handling of the infant takes place. An electrode can be moved from one part of the head to another simply by squeezing the cups slightly; this produces a leak and the electrode falls off, it can then be "sucked on" in a new position. Turning off the pump at the end of the recording allows all electrodes to fall off.

It has been found important to wash the electrodes immediately after use and again attach to the vacuum pump in order to remove any small particles which might cause blockage of the fine polythene tube.

Records have been taken in this way without signs of discomfort to the baby, the marks of the electrodes disappearing within half an hour.

Figure 2 shows electrodes in position on a 3½ lb. oedematous baby three days after birth.

Our thanks are due to Dr. Beryl Corner, Consultant Physician of the Bristol Maternity Hospital and to the staff in charge of the Premature Unit in that Hospital for their permission and co-operation in this study.

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Reference: COOPER, R. and WALTER, V. J. Suction cup electrodes. *EEG Clin. Neurophysiol.*, **1957**, *9*: 733-734.

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SOCIETY PROCEEDINGS

THE DANISH EEG SOCIETY

Secretary: B. HARVALD
University Institute for Human Genetics, Copenhagen, Denmark

September 25, 1956

Queen Louises Hospital for Children

Round table conference: EEG in mental deficiency

1. **Electroencephalographic findings in 200 children with mental retardation. — SVEN BRANDT, Copenhagen.**

Eighty-six abnormal records were found with the following clinical relations: Complicating cerebral palsy alone: 11 cases. Complicating cerebral palsy and epilepsy: 13 cases. Complicating epilepsy alone: 34 cases. Children with a history of "cured" epilepsy: 4 cases. Hypothyroidism: 1 case. Mentally retarded children without epilepsy or cerebral palsy: 23 cases. In this last group diffuse abnormalities (slowing) were found in 14, paroxysmal abnormalities in 5, focal abnormalities in 2 and 6-14 per sec. positive spikes in 1.

2. **EEG in phenylketonuria. — SVEN BRANDT, Copenhagen.**

Abnormal EEG was found in 3 infants, all below 2 years of age at the time of examination, contrasting to normal EEG in 2 children older than 2 years.

One infant was electroencephalographically followed from the age of 11½ months until the age of 28 months. As long as frequent myoclonic or akinetic petit mal seizures were present, severe abnormalities were found in the records during waking state and sleep. Phenobarbital gave some clinical but no electroencephalographical improvement. Two and one half months of feeding on a very low protein diet gave no EEG improvement. About one year after cessation of this dietary experiment spontaneous normalization could be noticed in the waking EEG and periodic abnormal paroxystic patterns were left only during sleep. Epileptic symptoms were rare, but the child was severely mentally retarded.

The findings indicate that this metabolic disorder tends to change from an active phase during early infancy to an electroencephalographically less active phase. This is a development well-known from other degenerative cerebral disorders of infancy.

3. **EEG in tuberous sclerosis and juvenile amaurotic idiocy. — J. ELLEBJERG, Filadelfia Colony.**

In a patient with tuberous sclerosis slight diffuse abnormalities without epileptic paroxysms were found. A patient with juvenile amaurotic idiocy showed bilateral paroxysms of high voltage activity.

February 26, 1957

Institute of Neurophysiology, Copenhagen

1. **EEG in acute carbon monoxide poisoning. — M. LENNOX and P. BENDER-PETERSEN, Copenhagen.** (To be published in *EEG Clin. Neurophysiol.*).

2. **EEG during treatment with chlorpromazine ("Largactil"). — R. SOGARD JORGENSEN, Copenhagen.**

Twenty psychiatric patients, all males, were examined. Their ages were between 17 and 59 years. None of the patients were suffering from epilepsy; 300-1500 mg. of chlorpromazine were given a day.

In all patients EEG was recorded before treatment, 3-7 times during treatment and 2-3 times after withdrawal of chlorpromazine.

Before treatment 9 patients had totally normal EEG, in 11 patients different abnormalities were found.

During treatment the alfa activity was affected in 16 patients, being more regular and of higher amplitude; in 4 of these patients the frequency was lowered; 13 patients showed admixture of slow activity, 8 patients of fast activity. In 10 patients spikes, sharp waves or series of slow activity were demonstrated. In a patient with acute chlorpromazine poisoning (5 g.) homologous epileptic paroxysms were found. These, however, had disappeared after 5 days. In none of the patients focal abnormalities were provoked. After withdrawal of treatment no signs of abstinence were found.

3. **Epilepsy and spontaneous hypoglycemia in children. — SVEN BRANDT, Copenhagen.**

Four case histories of children with rare hypoglycemic periods were recorded, in which no endocrine dysfunction was found. Two patients gave signs of neurologic disorder by clinical examination, encephalography or EEG. The usual causes of spontaneous hypoglycemia are discussed. The hypothesis is offered that hypoglycemia may be an ictal epileptic manifestation of hypothalamic dysfunction similar to other epileptic vegetative seizures, e.g. hyperthermia.

4. **EEG in old age. — B. HARVALD, Copenhagen.** (To be published in *Acta psychiat., neurol. scandinav.*)

5. **Clinical and electroencephalographic studies in 399 patients with acute cranial traumas. — E. FRANTZEN, B. HARVALD and H. HAUGSTED, Copenhagen.** (To be published in *Acta psychiat., neurol. scandinav.*)

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III SOUTH AMERICAN CONGRESS OF ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY

Medellín, Colombia

July 8-11, 1957

General Secretary: Dr. ERNESTO BANCALARI

Enrique Barrón 1054, Lima, Peru

1. **The EEG in the cerebral vascular accident. — PAULO PINTO PUPO, ELIOVA ZUKERMAN, ROSA HELENA LONGO, MARIO L. MARTINEZ, RUBENS M. RIBEIRO and M. HELENA FRANCO DA ROCHA MOREIRA, Sao Paulo, Brazil.**

The authors made a review of the literature regarding the EEG changes due to cerebral anoxia and those which are found in experiments such as compression or ligation of the internal carotid artery, as well as in patients with cerebral vascular disease. They admit that anoxia is responsible for the appearance of signs suggestive of nervous tissue damage. These signs are depression and disorganization of the background activity followed by early appearance of delta waves which are then replaced by permanent depression of the background activity.

The authors studied the clinical signs and the EEG changes in 170 patients with cerebral vascular disease, apopletic or not (table I), and analyzed them according to the interval of time between the onset of the disease and the moment when the EEG was obtained (table II), according to the presence or not of arterial hypertension (table III), according to the patient's age (table IV), according to the progression of the disease to death (table V), according to the type of the lesion being mainly cortical or subcortical (table VI), according to the presence or not of signs of hemorrhage in the spinal fluid (table VII), according to the onset of the vascular disease (whether apopletic or not) (table VIII), according to the arteriographic findings (table IX) and, particularly, according to the sequence of EEG records obtained after the onset of cerebral vascular damage (table X).

From this analysis they observed: (1) the EEG showed evident signs of cerebral tissue damage in 72 per cent of the patients with cerebral vascular disease, whether the record was early or late; (2) there is an evident relationship between the interval of time after the onset of the stroke and the EEG pattern, there was a progressive disappearance of the signs indicating actual damage of the nervous tissue (disorganization of the background rhythm, delta waves) and persistence of signs which characterize residual lesions (depression of the cerebral electric activity). Signs of focal cerebral irritative lesion (sharp waves) were found in only a few cases and were found less frequently than convulsive signs; (3) there is no difference in the EEG between patients with or without arterial hypertension, between those with apopletic or non-apopletic strokes, between those patients with cortical or subcortical lesions; there is no difference between these groups when the analysis is made from the general point of view or when it is made in function of the period of time between the onset of the stroke and the EEG examination; (4) in 8 cases the EEG signs of cerebral tissue damage (delta waves) persisted one year after the stroke; all 8 patients presented arterial hypertension; (5) the patient's age did not influence the EEG record immediately after the stroke, neither did it show any influence on the clinical progression of the disease; (6) the EEG does not permit the differentiation between patients with or without hemorrhagic spinal fluid; (7) EEG records are similar in those cases in which there are no arteriographic changes and in those cases where the arteriograms revealed suggestive evidence for arterial thrombosis; (8) cases which progressed to death showed EEG with diffuse and marked changes, particularly the presence of rhythmic slow waves, which are suggestive of damage to centrencephalic centers; (9) the EEG was repeated several times in 52 patients (in 28 cases the EEG was repeated within 30 days and in 24 it was repeated after one month) and it was observed that clinical improvement appears when delta waves disappear; when delta waves persist this does not necessarily imply that the clinical signs will not improve (mental confusion, aphasia and hemiplegia); the disorganisation of the background rhythm runs parallel to the clinical course; the depression of cerebral electric activity, either local or diffuse, could persist even in cases in which the clinical signs have disappeared.

Each one of these findings are discussed and the authors conclude that these EEG findings are in accord with the general clinical pathological point of view that the stroke is the result of a local cerebral damage, more acute and more severe, resulting from a more diffuse cerebral vascular accident; there is no difference from the EEG point of view whether the etiological factor is arterial hypertension, rheumatic vascular disease, heart failure or disseminated arteriosclerosis; the only exception is probably the rheumatic embolism.

In the analysis of the EEG and the clinical signs, the authors call attention to the fact that when serial EEGs are obtained the changes in the record could originate in cerebral areas which do not produce clinical signs; on the other hand, subcortical lesions in the recovery stage could show clinical signs with no EEG changes. Both statements explain the apparent discordance existing between the results of EEG records and the clinical signs in these patients.

The EEG is therefore a functional test of great value in the diagnosis of cerebral tissue damage in cases with cerebral vascular accidents and in the study of their development, giving important data for the treatment and the prognosis of the disease. Although, it does not have the same value as the

clinical findings in evaluating the possible defects resulting from these vascular accidents.

2. **EEG in the cerebral vascular diseases. — Carlos Villavicencio, Chile and Nelly Ciofalo, Argentina.**

3. **EEG in cerebral vascular accident. — Carlos Villavicencio, Chile and Nelly Ciofalo, Argentina.**

4. **EEG in cerebral thrombosis. — Pedro L. Ponce, Venezuela.**

5. **EEG in cerebral vascular accident. — Aldo Imbriano, Argentina.**

6. **Role of the cerebellum in the localizing and jumping reactions. — Miguel Covian and Cesar Timo Jaria, Brazil.**

7. **The action of mechanical vibrations on the electroencephalogram. — E. Garcia-Austt and E. F. Migliario, Montevideo, Uruguay.**

On the brain of a curarized awaken cat mechanical vibrations of ultrasonic and sonic frequency were performed with a small caliber rod. This was applied directly on the cerebral cortex or it was introduced into the thalamus or posterior hipothalamus with a stereotaxic instrument.

It was established that subcortical structures are much more sensible than the cortex to the action of mechanical vibrations. A determined energy which when applied on the cortex did not produce local modifications, modified the electric activity of both hemispheres when it was applied to the thalamus or the hypothalamus.

These modifications consisted of the substitution of the fast wake rhythm for a sleep rhythm with the characteristic spindles, and in a higher grade by decreasing the general amplitude of the record.

The alterations were bilateral but with an ipsilateral predominance and were reversible at variable times.

These facts are connected with the physiology of sleep and experimental cerebral concussion.

8. **Chronaximetric studies in facial palsy. — Ernesto Bancalari and Gino Costa, Lima, Peru.**

Fifty seven cases of facial palsy ''a frigore'' were periodically studied from the clinical point of view as well as from the point of view of chronaxie values of the muscles involved. The following conclusions were reached:

1. 98.3 per cent of the cases had high chronaxie values during the evolution of the paralysis, and only one case (1.7 per cent) had normal values and recovered completely before 18 days.

2. In 80 per cent of the cases high values were found before 21 days after the onset.

3. The abnormal chronaxie values were not similar in the paralyzed facial muscles but on the contrary were of different magnitude.

4. It is very frequent (65 per cent) to find the chronaxie values of those muscles in the lower facial territory to be much greater (more than double) than those in the upper facial territory.

5. Although normal chronaxie values or low abnormal values correlate with good motor recovery, high values do not necessarily signify a bad prognosis.

6. Those cases with prolongued (more than 2 months) high chronaxie values of the peribuccal muscles had a strong predisposition toward facial hemispasm.

7. In our cases none of the cases of facial palsy that returned to normal chronaxie values went into hemispasm.

9. **Chronaximetric studies in radial palsy. — Gino Costa and Ernesto Bancalari, Peru.**

10. **EMG study of some reflex reactions in cerebral palsy. — M. A. Perlstein, M. Turner, N. Turner and H. Elam, Chicago, U.S.A.**

The authors report the results of EMG studies in flexor and extensor muscle groups of arms and legs in 13 spastic and 10 athetoid patients. The following measurements were made:

1. *At rest*: no activity was observed in 8 spastics and in 2 athetoids. Involuntary activity observed in 3 spastics was continuous and constant in location. On the other hand in 6 athetoids muscular activity was irregular in short and frequent outbursts of 1-2 sec. and 1-5 sec. intervals, with irregular and unpredictable changes in their location.

2. *Deep tendon EMG reflexes responses*: knee, ankle, bicipital jerks were of great amplitude and irradiated to antagonistic and distal group of muscles in 12 of 13 spastics. In two cases they were repetitive (clonus). In the athetoid group EMG reflexes responses where either localized to the muscle explored (5 cases) or with irradiation to antagonistic or distal group of muscles but in an unpredictable and variable pattern from one to another stimulation.

3. *Plantar cutaneous stimulation*: in the group of spastics EMG activity in the extensor of the toes group was detected in all the cases including in those in which no clinical Babinski sign was present. In the athetoid group equivocal or negative response was observed.

4. *Support reaction* : evoked by proprioceptive stimulation (forced hyperextension of wrist and fingers or ankle and toes) provoked in 11 spastics positive reaction consisting in simultaneous EMG activity in flexor and extensor groups of muscles. In athetoids it was positive only in 2 cases.

5. *Crossed reaction*: painful sensory stimulation provoked a positive EMG response in the controlateral side in 11 spastics and only in 3 athetoids.

6. *Tonic neck reactions*: passive and/or active movements of the neck evoked EMG activity in some of the groups of muscles explored in 9 spastics and 5 athetoids, and no reaction in 2 spastics and 5 athetoids.

7. *Positional changes* : from lying to sitting and/or standing positions provoked and increased EMG activity in 6 spastics and 6 athetoids. In the rest of the cases this reaction was not explored or the EMG was equivocal due to artefacts.

8. *Associated or irradiated reactions*: forced and voluntary activity of the controlateral and/or distant limb evoked an EMG irradiation in 10 spastics and 5 athetoids.

The action of some ''relaxant'' and ''ataraxic'' drugs were tested in 7 cases. Miltown and MR 710 (new compound of Abbott) diminished EMG activity in 1, 4, 5, 6, 7 and 8 responses (polysynaptic pathways ?) but did not affect very much the 2 and 3 responses (mono or disynaptic ?).

The authors concluded that the most important dif-

ferences between spastics and athetoids from the EMG point of view were to be found in the resting activity, the deep tendon reflex responses, the support reaction, the plantary reflex, the crossed reaction and the tonic neck reaction. That both categories share some pathophysiological mechanisms by which postural changes and associated reactions are exaggerated.

The importance of these studies in correlation to anatomic and clinical findings is stressed in order to get a better understanding of the pathophysiology of the different groups of cerebral palsy and possibly to choose the convenient therapeutic approach.

11. Electrodiagnostic studies in poliomyelitis: electromyography chronaxy and strenght-duration curves. — M. Turner and H. Núñez, Buenos Aires, Argentina.

Electromyographic examinations by means of needle and superficial electrodes were made in a group of 35 poliomyelitic patients, 6 within the first month after the onset of the disease, 17 within the first year and 12 from 1 to 15 years of evolution.

The most constant and early EMG findings were: 1. — Curves with smooth interference and individual spike potentials recorded even during a maximum effort of contraction, which are due to the reduction of the motor unit population. 2. — The ''giant potentials'' (5 to 10 mV.) that appeared even in the cases examined during the first month of the disease, but may persist in later periods. For this reason one may suppose that these phenomena have their origin in ''hypersynchronism'' of undamaged spinal cord motor-neurons rather than in hypertrophic muscular compensation. 3. — The ''fibrillation potentials'' (short potentials of 0.1 to 1 msec. and a characteristic high pitched noise in the loudspeaker) were not evident in any case prior to the first month of evolution. Hence, it does not seem to be a very early sign and would depend on the autorhythmicity and hyperirritability of the denervated muscular fibers. These potentials persisted in the cases with 11 years of evolution and did not have, apparently, any relation with the severity of the injury. 4. — The complex polyphasic potentials, of long duration (10-14 sec.) and irregular morphology were detected in the cases of positive recovery and in the later periods too. These would depend on the process of reinervation by ramification of the terminal axons of the undamaged neurons and would be the bioelectrical expression of new motor units whose functioning would be somewhat asynchronous. These potentials would constitute a good prognosis because they would indicate that the disease is in regression.

The chronaximetric examinations in series proved valuable in following the evolution and in establishing a prognosis. The rheobases varied in plus or minus without connection with the process. The intensity-duration curves were characterized by being broken, denoting fibers of different excitability, and being diverted upward and to the right, as a consequence of the loss of ability to respond to the excitation of short duration. The curves made by excitation through the motor points and through the motor nerves, revealed a greater separation and an inversion of their mutual relations. After the third month, if the evolution was favourable, a return to normal was observed, with a descent of both curves.

One may conclude that the combined electrodiagnostic method is a very valuable procedure in the diagnosis and prognosis of poliomyelitis.

12. Complex electrographic structure of temporal epilepsy. Its determination by deep electrography. — Elio García-Austt, Jaime Gogacz, Jorge San Julian, Eduardo Vigil, L. Perez Achard and Roman Arana, Uruguay.

Patients with temporal epileptogenic foci were studied with different types of electrodes: scalp, nasopharyngeal, sphenoidal, cortical and deep intracerebral.

A two part operation was practiced on the patients for surgical extirpation of the focus. In the first operation a craniectomy was practiced and cortical and deep electrodes were placed up to 24-32 distributed in the surface in the depth of the temporal lobe and on the orbital surface of the frontal lobe. In the second operation carried out 24 hours later the electrodes were removed and a large temporal lobectomy was performed. The temporal epileptogenic foci which was a single one in the recording obtained with the scalp, nasopharyngeal and sphenoidal electrodes happened to have a complex electrographic structure when studied with cortical and deep electrodes. In all of these cases several spike foci existed, which were located on the inferior face of the temporal lobe, on the uncus and in the amygdaloid region and discharged asynchronously. Among these foci there always was a more active one with polyphasic spikes higher in voltage and more constant and with a greater tendency to rhythmical discharge.

This focus was preferentially located in the amygdaloid region or in the uncus. The discharge recorded on the scalp was evident only when two or more deep foci synchronized their activity. This always happened when a wide area of the temporal lobe was synchronized. The form of the discharge recorded on the scalp was always more simple.

Patients were studied awake and in spontaneous or induced sleep with Metrazol activation, electrical cortical and deep stimulation, and with sensory stimulation. Metrazol highly increased the duration and intensity of the discharges synchronizing the activity of several of the epileptogenic areas. Electrical stimulation produced the same result. When because of these effects a clinical attack was induced the synchronization was also produced in a very wide area of the temporal lobe and occasionally in the orbital surface of the frontal lobe.

With this method it was possible to establish the complex electrographic structure of the focus constituted by a group of epileptogenic areas. The precise delimitation of these areas constituted a decisive criterion for surgical conduct of the surgical intervention.

This group of psychomotor epilepsies represented from the electrographic point of view a real multifocal type of temporal lobe epilepsy.

13. Our electroencephalographic experience in temporal epilepsy. — Julio Ghersi and coll., Argentina.

14. The temporal focus in childhood epilepsy. — Angel Monti, Argentina.

15. The EEG in the tumours of the III ventricle. — Carlos Villavicencio, Chile and Nelly Ciofalo, Argentina.

16. The EEG in the diagnosis and prognosis of cerebral abscess. — Paulo Pinto Pupo, A. Matos Pimentta and O. Barini, Sao Paulo, Brazil.

The authors have obtained electroencephalographic studies in cases of cerebral abscess since 1951; these records were always obtained before any neurosurgical treatment was carried out and were repeated several times after the surgical intervention. The authors call attention to the important data that the EEG can offer to the diagnosis of cerebral abscess and to the prognosis of the patients who are operated on.

Of 22 patients 20 had EEGs taken previously to the surgical treatment (among which 17 with repeated EEG after the operation) and 2 had EEGs taken only after the operation. These cases were studied clinically and electroencephalographically and the diagnosis was confirmed by arteriograms and by the surgical treatment. All patients were operated on and received antibiotics.

In the group of patients with EEGs obtained before the surgical treatment, the authors found diffuse changes in the records of the 20 patients (100 per cent), and focal changes consisting mainly in delta waves of 0.5-5-3 c/sec. and of potential amplitude of 400-500 μV in 19 cases; focal depression of the background rhythm in 11 cases; epileptogenic foci were found only in 2 cases. These findings very slow delta waves and focal depression of the basic rhythm represent very important data for the diagnosis, particularly when studied in relation to the clinical picture.

In the group of patients who had clinical and EEG examinations after the operation, the EEG records having been repeated during a period of time from one to 60 months, the authors found signs of active convulsive focus in 10 out of 17 patients. In the opinion of the authors this incidence is very high and it is in accordance with the high incidence of epilepsy following cerebral abscess. The length of time between the operation and the onset of the focal activity varied from one to 25 months. Out of 10 patients with focal activity and with clinical epilepsy, only 2 patients had presented focal activity before to the ''healing'' of the abscess. The authors discuss this problem and believe that the healing process, which is a slow mechanism, is responsible for the onset of these clinical and electroencephalographic manifestations.

In the same group only 4 patients had normal EEGs during all the follow-up period; 2 patients had normal EEG for 5 and 15 months, but developed focal activity later on. 3 other patients had signs of damage to the nervous tissue (delta waves) from one to 3 months after the operation (patients with convulsive seizures or still with signs of abscess in evolution).[1] In 6 cases there was some focal depression of the EEG after the operation and in 4 cases there were slight changes of the background rhythm, which were due to the healing process and were not correlated to any clinical signs.

The authors conclude that the EEG is a very important auxiliary method for the diagnosis of cerebral abscesses for the prognostic evaluation of those cases treated surgically. When the EEG shows disappearance of acute signs of cerebral involvement, a good prognosis can be expected. It may also show the early formation of an active convulsive focus, which is not only important for the prognosis, but also permits to institute a prophylactic anticonvulsive therapy.

1 For several reasons the EEG changes found during the first month following the surgical treatment were not included in the present paper.

17. Pharmacologic action and EEG response of amphiliactil on the vestibular nerve. — Abraham Mosovich and J. Tato, Argentina.

18. Electroencephalographic studies in poliomyelitis. — M. Turner and H. Núñez, Buenos Aires, Argentina.

Thirty six EEG controls were made in 31 children from 6 months to 10 years of age in the recent epidemic of poliomyelitis in Buenos Aires (summer 1956).

Nineteen normal and 15 abnormal EEG were obtained. The abnormalities in 14 cases were hypersynchronous delta waves, bilateral, symmetrical and synchronous, diffuse or localized preferentially in the occipital and temporal areas. In only one case a generalized depression was observed.

The EEG abnormalities were more frequent in the acute period of the illness (less than 1 month). But they were also found in the post-acute periods (more than 3 months of evolution) in 9 cases, 6 of which were affected by polioencephalomyelitis.

In the group of children with respiratory forms of the disease (bulbar and high spinal) only one abnormal EEG was found in 11 cases; these cases were treated very early with therapeutic measures (pulmotors, rocking beds, bronchial aspiration, tracheotomy, etc.); they had not suffered from encephalitic symptoms and they were recorded in the post-acute stages.

It is inferred that the pathological manifestations in the EEG records of poliomyelitic cases seem to be related to lesions of the subcortical formations (brain stem and diencephalon), can be correlated with encephalitic symptoms and that they are more frequent in the acute stages of the disease although they can persist in the post-acute stages. These facts may justify the use of neurolytic therapies (neurolysis, artificial hybernation, etc.) in the acute period of polioencephalomyelitis, and the EEG controls in the post-acute stages to detect and explain mental and/or convulsive disorders.

No higher incidence of the encephalitic manifestations seems to exist in the respiratory forms (high spinal and bulbar) when the anoxia was prevented by correct and opportune therapeutic measures.

In every epidemic of poliomyelitis there is a remarkable interest for this EEG research to be correlated with clinical and virologic characteristics.

19. The EEG in detection of epilepsy in the Air Forces. — Ernesto Bancalari and G. Garcia V., Peru.

20. Enuresis and electroencephalography. — Ernesto Bancalari and A. Garcia V., Peru.

21. Use of paraldehide in the EEG of children. — Pedro Ponce, Venezuela.

The author presents the good results of Paraldehide injected intramuscularly in 100 cases of behaviour problem, which were difficult to handle or in agitated children who were resistant to other sedatives. All the records obtained were very clear and completely free of rapid frequency artifacts. Although there were no complications the author re-

commends a previous examination of hepatic and respiratory functions.

22. **The EEG in syphilitic encephalitis. — ALVARO CALDERÓN, Colombia.**

23. **Clinical electroencephalography. — ALDO IMBRIANO, Argentina.**

24. **Electroencephalographic studies in men spraying chloride insecticidis (Dieldrin).**

ANNOUNCEMENT

AMERICAN ELECTROENCEPHALOGRAPHIC SOCIETY

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At the annual examinations held in St. Louis, Missouri, October 1, 1957, the following four candidates were certified by oral and written examinations.

Charles Chaskiel Grossman	Pittsburgh, Pennsylvania
Michael G. Saunders	Winnipeg, Manitoba, Canada
Fernando Torres	Minneapolis, Minnesota
William P. Wilson	Durham, North Carolina

The 1958 examinations will be held in Baltimore, Maryland, on Tuesday, June 10th, before the annual meeting of the American EEG Society in Atlantic City. Formal application should be made to the undersigned. The closing date for such applications will be February 28, 1958. The written examination will be held in April 1958.

The present Board consists of:

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Booklets carrying the names and addresses of those qualified by the Board may be obtained by writing to the Chairman, Robert S. Schwab, M.D., Massachusetts General Hospital, Boston 14, Massachusetts.

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BOOK REVIEWS

Edited by CHARLES E. HENRY

ATLAS CEREBRI HUMANI. THE INNER STRUCTURE OF THE BRAIN

E. LUDWIG and J. KLINGLER

S. Karger, Inc. Basle, Switzerland, price: 75 swiss francs

Little, Brown and Company, Boston and Toronto, price: $18.50, 136 pp.

For many who consider macroscopical anatomy to be a closed chapter, publication of the "Atlas Cerebri Humani" by Ludwig and Klingler must have come as a stimulating and unexpected surprise. For this work is rooted in the best tradition of Vesalian Anatomy and seems to be permeated by the spirit of the Old Master's "Fabrica" and yet it is truly modern in advancing significantly our knowledge of the inner architecture of the human cerebrum.

The writer of this review, who as a medical student had the privilege of being taught the principles of neuroanatomy by the two authors of this book, knows how uncompromisingly they were dedicated to the study of morphology, being anatomists in the true old sense of the word, for whom the study of form and structure still remained the foremost concern of their investigative effort. This essential concern with the study of morphology as such is the secret of this work's success. It brings home to us, how incomplete our traditional methods of studying and teaching neuroanatomy really are and how they fall short of telling us the full story of the inner architecture of the human brain. Since for the authors of this Atlas the problem of brain anatomy was essentially one of morphology, they put all their efforts into developing a method of study, which would satisfy a morphologist's criteria of disclosing the three-dimensional structure of the organ without undue disruption of natural structural and topographical relationships. In the quest for such a method the authors were able to overcome a basic difficulty with which the study and teaching of brain anatomy had hitherto always been burdened. This difficulty resides in the apparent impossibility of applying to the brain the principles of classical anatomical dissection techniques as used for other organ systems and which strive to demonstrate the natural structural and topographical relationships of the component parts of a region or organ by following the inherent planes of cleavage and by avoiding to disrupt more than absolutely necessary the continuity of individual anatomical structures. For the study of the central nervous system this method was considered as technically impossible and the substitute of cutting the brain into a series of usually frontally oriented slices was therefore adopted as the most customary method of study. This forces the student to rely on his ability to translate in his own mind a sequence of two-dimensional slices into an integrated whole organ, a mental effort, which at best meets with only partial success.

It is therefore a notable achievement that Klingler was able to develop a macroscopical dissection technique which permits application of the principles of classical anatomical dissection to the study of the human brain. Attempts to do this are not new. W. Hultkrantz in Germany and A. T. Rasmussen in the United States have done it with notable success. However, the method developed by Klingler, by which the formaline-fixed brain is first frozen and then allowed to thaw, renders macroscopical dissection much more practicable than was hitherto possible, even to the point where it may be performed as a routine teaching method in the anatomy laboratory.

An excellent collection of brain specimens beautifully dissected with this technique serves as the illustrative material for the Atlas. All those accustomed to think of the anatomy of the brain in terms of a series of frontal sections will find that virtually all the fiber tracts and nuclear masses visible in histological slides can be dissected out clearly and can thus be demonstrated in their natural three-dimensional relationship with neighboring structures.

In a series of 100 tables all the main fiber tracts and nuclei of the cerebrum are shown without cutting in any unnatural way through their mutual structural and topographical relationships. Each illustration consists of a large, high quality black-and-white photograph of a dissected specimen. Below each photograph is a smaller drawing of the same specimen in which all relevant structures are labelled with their latin name as listed in the Parisiensia Nomina Anatomica (P.N.A., officially adopted by the International Congress of Anatomy, Paris, 1955). The study of these tables discloses relations which would be hard, if not impossible to visualize with other methods and would be even more difficult to describe accurately in a text.

The short introductory text to this Atlas is written in German, English, French and Spanish. It describes Klingler's dissection method and gives some comments on the nomenclature and the identity of certain structures shown in the tables. It does not,

however, represent a systematic text of neuroanatomy. This Atlas is not meant to supplant neuroanatomy textbooks, but to serve as a visual guide, which may be used in conjunction with any good neuroanatomical text. Its finest purpose, however, will be fulfilled if it can induce those engaged in teaching neuroanatomy to take a fresh look at this problem and to try their hand at the Klingler-method of brain dissection. To bring this method into the classrooms of our medical schools should not be impossible, since it has already been done for many years with notable success at the University of Basle, Switzerland, under the guidance of the authors of this Atlas.

P. GLOOR, M.D.

ELECTRODIAGNOSIS AND ELECTROMYOGRAPHY

Edited by SIDNEY LICHT

Elizabeth Licht, New Haven, Conn. 1956. 272 pp. $10.00

It is always more difficult to be fair in a review of a book where there are multiple authors and this book, Electrodiagnosis and Electromyography, is an excellent example of this. There are twelve authors covering the ten chapters and two appendix sections. The first chapter on the history of electrical effects in living tissue and electrodiagnosis is surely the best one in the book. Most historical chapters are rather dull reading but this one is so arranged that anyone interested in the field of electrophysiology would read it carefully and completely since it covers the significant developments by physicists such as Volta and great scientists such as Galvani and integrates the whole history with the development of the recording of electro-physiological phenomena in nerve and muscle up to the present time. This chapter indeed should be recommended reading for students of electroencephalography.

The second chapter concerning apparatus is oriented towards the electro-diagnosis that is covered in most up to date departments of physical medicine. It rapidly covers the fundamentals and spends considerably more detail on such things as chronaxie, dermo-meters and electrical stimulators. The part on the cathode ray oscilloscope is very good and information that is of interest to the electro-physiologist concerning tape recorders and loud speakers is excellent. The chapter would be stronger if more details of the standard electromyographic unit were included.

An outstanding chapter in this book is that on the physiology of skeletal muscle by Ernst Fischer which covers both the anatomical, biochemical and electrical events in an unusually clear, coordinated manner. A most complete bibliography is included.

The chapter on motor points and the technique of electrodiagnosis are complete but not unusual.

The chapter on chronaxie is a bit over-detailed since the following one on strength duration curves is perhaps of far greater importance and interest to the clinician who is using electrical apparatus and doing tests of muscle and nerve function.

The chapter on progressive and alternating currents is more difficult reading and perhaps more theoretical than practical.

The chapter on electromyography is excellent except that it carries far too few illustrations because it reports, according to the title, one of the major features of the book. The authors of this chapter are to be congratulated in illustrating clearly the application of inkwriters to electromyography under the section called kinesiology studies. Again, examples mentioned in the test were not shown in illustrative form.

Since this book was put together largely by experts in the field of physical medicine, and since electromyography and electronic diagnosis is largely dependent clinically on such departments, it would seem that the appendices concerning electroencephalography and electroretinography were not necessary in this book. These two chapters are the weakest and most inadequate in this book and, like the human appendix, in most instances might well be taken out. Because of the number of excellent sections in this book it will be a very valuable asset to any clinical neurophysiological laboratory.

Robert S. SCHWAB, M.D.

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INDEX TO CURRENT LITERATURE

Edited by CHARLES HENRY
Institute of Living, Hartford, Conn. U.S.A.

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